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ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection

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ABSTRACT

Helicobacter pylori **is a prevalent, global infectious disease that causes dyspepsia, peptic ulcer disease, and gastric cancer. The American College of Gastroenterology commissioned this clinical practice guideline (CPG) to inform the evidence-based management of patients with *H. pylori* infection in North America. This CPG used Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to systematically analyze 11 Population, Intervention, Comparison, and Outcome questions and generate recommendations. Where evidence was insufficient or the topic did not lend itself to GRADE, expert consensus was used to create 6 key concepts. For treatment-naive patients with *H. pylori* infection, bismuth quadruple therapy (BQT) for 14 days is the preferred regimen when antibiotic susceptibility is unknown. Rifabutin triple therapy or potassium-competitive acid blocker dual therapy for 14 days is a suitable empiric alternative in patients without penicillin allergy. In treatment-experienced patients with persistent *H. pylori* infection, "optimized" BQT for 14 days is preferred for those who have not been treated with optimized BQT previously and for whom antibiotic susceptibility is unknown. In patients previously treated with optimized BQT, rifabutin triple therapy for 14 days is a suitable empiric alternative. Salvage regimens containing clarithromycin or levofloxacin**

ACG Clinical Practice Guideline

Treatment of *H. pylori* Infection in North America

	Treatment Naïve	*Treatment-Experienced (Salvage)*		*Penicillin Allergy*
Regimen		Empiric	Proven antibiotic sensitivity	
Optimized Bismuth Quadruple	☑☑☑	☑☑	☑☑	☑☑☑ *
Rifabutin Triple	☑☑	☑☑	☑☑	
Vonoprazan Dual	☑☑	?	?	
Vonoprazan Triple			☑☑	
Levofloxacin Triple			☑☑	

☑☑☑ Recommended ☑☑ Suggested ? May be considered when other treatments are not options

* When Bismuth Quadruple Therapy not an option, consider referral for formal penicillin allergy testing and/or desensitization

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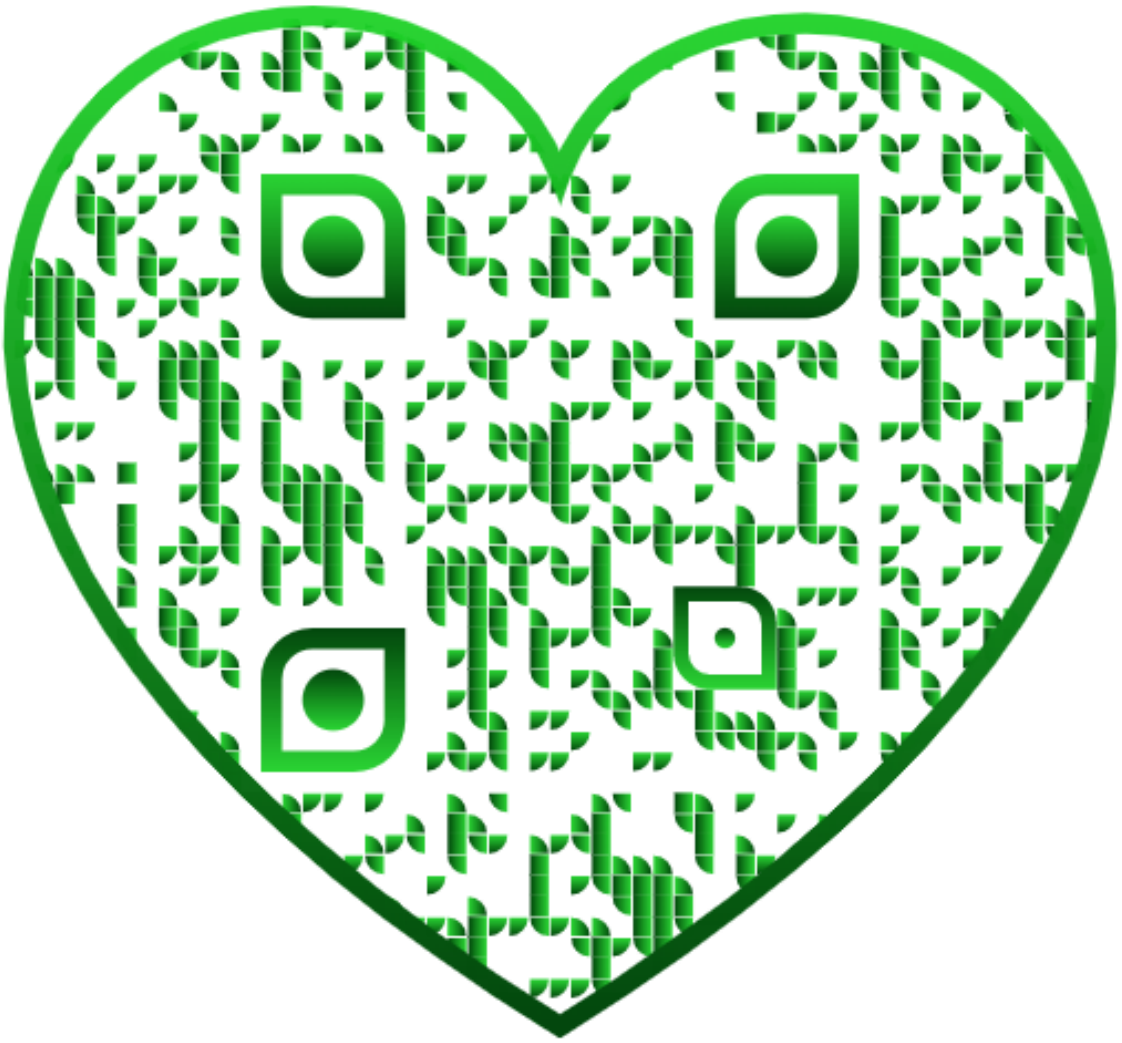

should only be used if antibiotic susceptibility is confirmed. The CPG also addresses who to test, the need for universal post-treatment test-of-cure, and the current evidence regarding antibiotic susceptibility testing and its role in guiding the choice of initial and salvage treatment. The CPG concludes with a discussion of proposed research priorities to address knowledge gaps and inform future management recommendations in patients with *H. pylori* infection from North America.

KEYWORDS: peptic ulcer; gastric cancer; dyspepsia; antibiotics; antibiotic resistance; salvage therapy

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D362; http://links.lww.com/AJG/D363.

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INTRODUCTION

Helicobacter pylori is a Gram-negative, spiral-shaped bacterium that has adapted to survive in the harsh acidic environment of the human stomach. *H. pylori* remains one of the most common chronic bacterial infections of humans worldwide (1). It is the leading cause of infection-associated cancer globally (2) and is categorized by the World Health Organization International Agency for Research on Cancer as a group I (definite) carcinogen because of its causal association with gastric cancer. All individuals who do not spontaneously clear the infection will develop chronic gastritis (3). Most infected individuals will remain asymptomatic and develop no meaningful clinical consequences. However, many will develop a wide range of benign or malignant clinical consequences as described later in this document.

Diagnostic testing for *H. pylori* has been discussed in detail in previous clinical practice guidelines (CPGs) and reviews (4,5). Because there have been little new data in the interim, we have elected not to review standard testing modalities (e.g., fecal antigen testing, breath testing, and serology) in this guideline. However, testing for *H. pylori* antibiotic sensitivity profiles has seen recent advances and implementation into clinical practice. Antibiotic sensitivity testing has grown beyond traditional culture and sensitivity to include modern molecular techniques that identify *H. pylori* gene mutations commonly associated with antibiotic resistance. Accordingly, we discuss the current level of evidence for antibiotic sensitivity testing in the context of treatment selection for *H. pylori* infection among treatment-naive and treatment-experienced individuals. We also discuss the critically important, but too often overlooked, issue of post-treatment testing to confirm *H. pylori* eradication.

The primary purpose of this ACG CPG is to provide practical, actionable advice on the treatment of *H. pylori* infection in North America. These guidelines are presented in the format of statements that were deemed to be clinically important by the content authors. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process was used to assess the quality of evidence for each statement (Table 1). The quality of evidence is expressed as high (we are confident in the effect estimate to support a particular recommendation), moderate, low, or very low (we have very little confidence in the effect estimate to support a particular recommendation) based on the risk of bias of the studies, evidence of publication bias, heterogeneity among studies, directness of the evidence, and precision of the estimate of effect (2). A strength of recommendation is given as either strong (recommendations) or conditional (suggestions) based on the quality of evidence, risks vs benefits, feasibility, and costs considering perceived patient-based and population-based factors (5). Furthermore, a narrative evidence summary for each section provides important definitions and further details for the data supporting the statements. The guideline is structured in the format of key concepts, recommendations, and summaries of the evidence. Key concepts are statements that are not amenable to the GRADE process, either because of the structure of the statement or the available evidence. In some instances, key concepts are based on extrapolation of evidence and/or expert consensus.

This guideline used GRADE methodology to evaluate treatment options for patients with *H. pylori* infection. We summarize treatment recommendations for patients with active *H. pylori* infection, as confirmed by a nonserological test, who have not been previously treated (i.e., "treatment-naive" patients) and those with persistent infection despite previous attempt(s) at eradication (i.e., "treatment-experienced" patients).

Readers will notice substantial changes from the recommendations offered in the 2017 ACG CPG (6). These changes were largely motivated by important new data from North America including:

1. Rising rates of resistance to key antibiotics used to treat *H. pylori*, including clarithromycin and levofloxacin. This has led to reduced effectiveness of commonly used treatment regimens that contain these antibiotics.
2. Studies that have been conducted with novel treatment regimens featuring new antibiotic options (i.e., rifabutin) or more potent, next-generation gastric acid-suppressing agents (i.e., potassium-competitive acid blockers; PCABs) in treatment-naive individuals.

As in previous versions, recommendations were based on the current, best available evidence with prioritization of evidence from studies conducted in North America. When unavailable, recommendations were based on studies conducted in other parts of the world and expert consensus.

METHODS

The guideline panel members were selected based on their clinical, scientific, and/or methodological expertise. Panel members included gastroenterologists with expertise in the diagnosis and treatment of *H. pylori* infection (W.D.C., S.C.S., D.R.M., S.F.M., and C.W.H.) and 2 GRADE methodologists (K.B.G. and S.G.). The guideline panel formulated clinically relevant questions suitable for methodological review. An experienced medical librarian assisted with relevant literature searches including EMBASE, MEDLINE, Cochrane, ClinicalTrials.gov, and PubMed. The guideline panel also reviewed the reference sections of available systematic reviews and meta-analyses. For each guideline question, the evidence review team conducted a

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Table 1. GRADE criteria

Strength of recommendation	Criteria
Factors influencing the strength of the recommendation include the quality of the evidence, clinical and patient-reported outcomes, risk of harm, and costs/healthcare resource utilization.	
Strong	Strong recommendations are offered when the desirable effects of an intervention clearly outweigh the undesirable effects. Implications from a patient and clinician perspective: Patients: Most individuals in this situation would prefer the recommended course of action, and only a small proportion would choose an alternative. Clinicians: Most patients should receive the recommended course of action or an alternative with similar strength of recommendation.
Conditional	Conditional recommendations are offered when trade-offs are less certain—either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced. Implications from a patient and clinician perspective: Patients: Some individuals would want the suggested course of action, whereas others may not. A discussion regarding pros, cons, and available alternatives is appropriate to reach an individualized patient-specific decision. Clinicians: A shared decision-making model through a discussion regarding the available evidence and alternative options is appropriate, taking into consideration the values and preferences of the patient.
Quality of evidence	**Criteria**
High	We are very confident that the true effect closely aligns with that of the estimate of the effect.
Moderate	We have a moderate level of confidence in the estimate of effect. It is likely that the true effect is close to the estimate of the effect.
Low	Our confidence in the effect estimate is limited. The true effect could differ from the estimate of effect.
Very low	We have very little confidence in the effect estimate. The true effect may be substantially different from the estimate of effect.

systematic review based on specific Population, Intervention, Comparison, and Outcome (PICO) questions developed by the guideline panel (see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D362). We included individual randomized controlled trials (RCTs), systematic reviews, meta-analyses, and network meta-analyses. Included trials evaluated treatment regimens of between 5 and 14 days' duration. The populations of interest included both treatment-naive and treatment-experienced adult (≥18 years) patients with active *H. pylori* infection. Interventions considered were proton pump inhibitor (PPI)-clarithromycin triple therapy, bismuth quadruple therapy (BQT), concomitant therapy, rifabutin triple therapy, PCAB dual therapy, PCAB triple therapy, quinolone-based therapy, high-dose PPI dual therapy, susceptibility-guided therapy, and probiotics. Comparators included PPI-clarithromycin triple therapy, BQT, and empiric (i.e., non–susceptibility-guided) therapy. Individual components of treatment regimens and the respective dosing/frequency in the intervention and control arms were as defined in individual studies; these were recorded for data evaluation purposes. Outcomes considered were eradication rate in intention-to-treat (ITT) and per-protocol (PP) analyses, compliance with treatment, and rates of adverse events.

The guideline methodologists performed meta-analysis when more than 1 study contributed data for the same intervention and outcome. They combined the dichotomous outcomes to obtain a relative risk (RR) and 95% confidence interval (CI). For the meta-analysis, methodologists used the generic inverse variance method of weighting and applied the random-effects model. They assessed statistical heterogeneity with the I^2 index and χ^2 statistic. They used RevMan software for all statistical analyses and the Cochrane risk-of-bias tool to assess the risk of bias in the included studies.

Each recommendation statement has an associated assessment of the certainty of evidence (high, moderate, low, or very low) and strength of recommendation (strong or conditional) based on the GRADE process. Treatment statements "recommend" a treatment in cases of a strong recommendation and "suggest" a treatment in cases of a conditional recommendation. Table 2 provides a summary of the recommendations. A number of topics were felt to be of clinical relevance for providers but were not felt to be amenable to or to merit a formal recommendation according to GRADE. These topics are presented as key concepts. Table 3 provides a summary of the key concepts discussed in this guideline.

EPIDEMIOLOGY

Key concept

1. The prevalence of *H. pylori* infection in North America is decreasing over time but remains substantial at 30%–40%. The infection is typically acquired in childhood and is more prevalent among non-White races and ethnicities, those living in crowded or poor sanitary conditions, and early generation immigrants from countries where *H. pylori* is endemic.

H. pylori infection is the most common chronic bacterial infection of humankind with a global prevalence of more than 40% (7). *H. pylori* has coevolved with humans over the past 100,000 years, and *H. pylori* subpopulations mirror human migration patterns, with 4 principal geographic reference groups: African, American (Amerindian), Asian, and European (8). The population structure of worldwide *H. pylori* genomes has recently been elucidated in the *H. pylori* Genome Project (9). The global

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Table 2. Guideline recommendations

Recommendations for treatment-naive patients with *Helicobacter pylori* infection
1. In treatment-naive patients with *H. pylori* infection, optimized BQT is recommended as a first-line treatment option (strong recommendation; moderate quality evidence)
2. In treatment-naive patients with *H. pylori* infection, rifabutin triple therapy is suggested as a first-line treatment option (conditional recommendation; low quality evidence)
3. In treatment-naive patients with *H. pylori* infection, dual therapy with a PCAB and amoxicillin is suggested as a first-line treatment option (conditional recommendation; moderate quality evidence)
4. In treatment-naive patients with *H. pylori* infection and unknown clarithromycin susceptibility, PCAB-clarithromycin triple therapy is suggested over PPI-clarithromycin triple therapy (conditional recommendation; moderate quality evidence)
5. In treatment-naive patients with *H. pylori* infection, concomitant therapy is not suggested over bismuth quadruple therapy (conditional recommendation; low quality evidence)
Recommendations for treatment-experienced patients with persistent *H. pylori* infection
6. In treatment-experienced patients with persistent *H. pylori* infection who have not previously received bismuth quadruple therapy, optimized bismuth quadruple therapy is suggested (conditional recommendation; very low quality of evidence)
7. In treatment-experienced patients with persistent *H. pylori* infection who have previously received PPI-clarithromycin triple therapy, optimized bismuth quadruple therapy is suggested (conditional recommendation; low quality of evidence)
8. In treatment-experienced patients with persistent *H. pylori* infection who have received bismuth quadruple therapy, rifabutin triple therapy is suggested (conditional recommendation; low quality of evidence)
9. In treatment-experienced patients with persistent *H. pylori* infection who have not previously received optimized bismuth quadruple therapy, optimized bismuth quadruple therapy is suggested over quinolone-based therapy (conditional recommendation; low quality of evidence)
10. In treatment-experienced patients with persistent *H. pylori* infection, levofloxacin triple therapy is suggested in patients with known levofloxacin-sensitive *H. pylori* strains and when optimized bismuth quadruple or rifabutin triple therapies have previously been used or are unavailable (conditional recommendation, low quality of evidence)
11. In treatment-experienced patients with persistent *H. pylori* infection, there is insufficient evidence from North America to recommend high-dose PPI or PCAB dual therapy (no recommendation; evidence gap)
12. There is insufficient evidence to suggest that the use of probiotic therapy improves the efficacy or tolerability of *H. pylori* eradication therapy (conditional recommendation; low quality of evidence)
BQT, bismuth quadruple therapy; PCAB, potassium-competitive acid blocker; PICO, Population, Intervention, Comparison, and Outcome; PPI, proton pump inhibitor.

prevalence has declined from 58.2% between 1980 and 1990 to 43.1% in 2011 and 2020 but remains above 60%–70% in many low-resource settings (7).

H. pylori infection is typically acquired in early life, although later-in-life exposure has also been described among adults (e.g., military personnel) traveling to areas of high *H. pylori* prevalence (10,11). Chronic gastric infection is established in those who do not spontaneously clear the infection. The precise mode of transmission is unclear (12). Intrafamilial person-to-person vertical and horizontal transmission (e.g., gastric-oral and fecal-oral) are considered important. Community transmission may occur in resource-limited settings.

The principal clinical outcomes/sequelae include dyspepsia, peptic ulcer disease, and gastric adenocarcinoma. Additional associations include marginal zone B-cell lymphoma (MALToma), iron deficiency anemia, and idiopathic (autoimmune) thrombocytopenic purpura (6,13). In addition, *H. pylori* has been associated with a broad group of diseases, generally based on low-quality evidence, which is reviewed elsewhere and is beyond the scope of this guideline (14,15).

In North America, estimates of the prevalence of *H. pylori* range between 30% and 40% (1,7). *H. pylori* burden is disproportionately distributed by race and ethnicity, geography, socioeconomic status, and age, with an important birth cohort effect. Globally, there is a modestly higher prevalence in men than women (e.g., odds ratio 1.12, 95% CI 1.09–1.15) (16,17). In a study from the United States using 624,444 reference laboratory samples collected between 2005 and 2014, *H. pylori* seroprevalence was 24.8%. The highest seroprevalence (>30%) was in the southern United States (Texas, New Mexico) and the Southeast (18). In a broad study of prevalence in the US Veterans population from 1999 to 2018, the overall prevalence was 25.8% (n = 913,328) with substantial variation by race and ethnicity: non-Hispanic White 20.1%, Hispanic 36.7%, and Black 40.2% (19). These differences were accentuated in Hispanics and non-Hispanic Black individuals younger than 60 years when compared with non-Hispanic White individuals (34.4% and 40.7% vs 17.2%). There was an overall decrease in prevalence of 35.9% in 1999–2006 to 18.4% in 2013–18. There was modest variability in prevalence by geographic region (20%–40%), with the highest in the Southeast (>40%). Active *H. pylori* infection determined nonserologically demonstrated similar demographic patterns as *H. pylori* seroprevalence (18,19).

Immigrants transitioning from high-prevalence (e.g., Mexico and Central America) to low-prevalence regions generally have a higher infection prevalence, which may wane with subsequent generations (20). In a meta-analysis of immigration globally, foreign-born immigrants demonstrated lower *H. pylori*

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Table 3. Summary of key concepts

Key concepts
1. The prevalence of *H. pylori* infection in North America is decreasing over time but remains substantial at 30%–40%. The infection is typically acquired in childhood and is more prevalent among non-White races and ethnicities, those living in crowded or poor sanitary conditions, and early generation immigrants from countries where *H. pylori* is endemic.
2. The determination of when to test for—and treat—*H. pylori* should be viewed as a single, rather than 2 separate and distinct, decisions.
3. Clarithromycin- and levofloxacin-containing treatment regimens should be avoided in the absence of demonstrated macrolide and quinolone susceptibility, respectively.
4. All patients who are treated for *H. pylori* infection should undergo a test of cure with an appropriately conducted urea breath test, fecal antigen test, or biopsy-based test at least 4 wk after completion of therapy.
5. In treatment-experienced patients with persistent *H. pylori* infection that is confirmed to be clarithromycin-sensitive, PPI- or PCAB-clarithromycin triple therapy is suggested.
6. *H. pylori* antibiotic susceptibility tests using either phenotypic (culture-based) or molecular methods (polymerase chain reaction or next-generation sequencing) are becoming increasingly available in the United States. The incremental benefit of selecting an eradication regimen "tailored" to the antibiotic susceptibility profile compared with empiric selection of eradication therapy remains to be adequately defined and studied—for both treatment-naive and treatment-experienced patients. Based on expert consensus, we advise using antibiotic susceptibility testing whenever the choice of therapy remains unclear after taking into consideration any previous treatments for *H. pylori* infection, past antibiotic exposure more generally, and whether there is a documented history of penicillin allergy.

PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

prevalence than their counterparts remaining in the native nation (e.g., Japan and Mexico), but significantly higher *H. pylori* prevalence compared with the overall population of the destination nation (e.g., the United States) (20). Modest decreases were observed with longer duration of residence and in subsequent generations. This has important implications with respect to opportunistic screening for *H. pylori* among high-risk but asymptomatic persons (see below).

INDICATIONS FOR *HELICOBACTER PYLORI* TESTING AND TREATMENT

Key concept

2. The determination of when to test for—and treat—*H. pylori* should be viewed as a single, rather than 2 separate and distinct, decisions.

Testing for, and treatment of, *H. pylori* infection should be viewed as dependent rather than independent actions. *H. pylori* infection is an infectious disease with the potential for serious clinical consequences, including gastric cancer. Therefore, all patients with an indication for testing should be offered effective treatment if confirmed to have active infection—and should subsequently undergo a test-of-cure after treatment. The indications to test for and treat *H. pylori* infection are summarized in Table 4. The detailed supporting evidence for many of the indications to test for *H. pylori* infection is reviewed in the previous guideline. Newer information regarding testing indications is briefly summarized herein.

Indications for *H. pylori* testing and treatment for benign conditions

Dyspepsia, broadly defined as pain or discomfort in the upper abdomen, is common in primary care and referral settings. The "test-and-treat" approach for uninvestigated dyspepsia is reasonable in patients under the age of 60 years, without alarm features (vomiting, GI bleeding, unexplained iron deficiency, or weight loss), and without other indications for endoscopy (e.g., dysphagia, refractory heartburn, or regurgitation) (21). A lower age threshold of 50 years for the test-and-treat strategy may be appropriate in populations at higher risk of gastric cancer (see below) (22). For patients with dyspepsia along with alarm features, or risk factors for peptic ulcer (e.g., aspirin or nonsteroidal anti-inflammatory drug use) or gastric cancer (e.g., family history, immigration from a high incidence region), most, but not all, guidelines (23,24) recommend prompt endoscopy ,which not only identifies structural and histological abnormalities but may also be associated with greater patient satisfaction (25). In patients with functional dyspepsia, eradication of *H. pylori* infection only provides modest benefit. A recent meta-analysis identified 29 RCTs including 6,781 *H. pylori*–positive patients with functional dyspepsia (26). They reported that treatment of *H. pylori* was superior to control (PPI, prokinetics, or placebo) for symptom cure (RR of symptoms not being cured = 0.91; 95% CI 0.88–0.94, number needed to treat [NNT] = 14; 95% CI 11–21) and symptom improvement (RR 0.84; 95% CI 0.78–0.91, NNT = 9; 95% CI 7–17). The impact on symptoms was larger in patients with successful cure of *H. pylori* than in those who were not successfully cured of their infection (RR 0.65; 95% CI 0.52–0.82, NNT = 4.5, 95% CI 3–9). Overall adverse events (RR 2.19; 95% CI 1.10–4.37) and adverse events leading to withdrawal (RR 2.60; 95% CI 1.47–4.58) were reported more commonly with antibiotic therapy for *H. pylori*. Although clinical benefits of *H. pylori* treatment are modest, it bears emphasizing that eradication of *H. pylori* is one of the only potentially curative treatments for patients with functional dyspepsia (25), and reduces the risk of other downstream complications of chronic *H. pylori* infection. In both uninvestigated and functional dyspepsia, benefits range from symptom relief to decreased healthcare utilization. The benefits of the test-and-treat strategy for *H. pylori* in the Rome IV–defined functional dyspepsia subgroups of epigastric pain syndrome (epigastric burning and/or pain) and postprandial distress

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Table 4. Indications for *H. pylori* testing and treatment

Groups to test and treat for *H. pylori* infection[a]:
• Peptic ulcer disease: prior history or active disease
• Marginal zone B-cell lymphoma, MALT type
• Uninvestigated dyspepsia in patients who are under the age of 60 years
- In high-risk populations for gastric cancer, test and treat at age 45-50 years
• Functional dyspepsia
• Adult household members of individuals who have a positive non-serological test for *H. pylori*
• Patients taking long-term NSAIDs or starting long-term treatment with low-dose aspirin
• Patients with unexplained iron deficiency anemia
• Patients with idiopathic (autoimmune) thrombocytopenic purpura
• Primary and secondary prevention of gastric adenocarcinoma
- Current or history of gastric premalignant conditions (GPMC)[b]
- Current or history of early gastric cancer resection
- Current or prior history of gastric adenocarcinoma
- Patients with gastric adenomas or hyperplastic polyps[c]
- Persons with a first degree relative with gastric cancer[d]
- Individuals at increased risk for gastric cancer including certain non-White racial/ethnic groups, immigrants from high gastric cancer incidence regions/countries, hereditary cancer syndromes associated with an increased risk for gastric cancer[d]
- Patients with autoimmune gastritis

[a]In the absence of contraindications, *H. pylori* treatment should be offered to all patients with active *H. pylori* infection, as indicated by a positive non-serological test. Serological testing is not recommended in low-prevalence populations in the absence of a high pre-test probability (e.g., peptic ulcer).
[b]GPMC includes atrophic gastritis, intestinal metaplasia, and dysplasia.
[c]Patients with adenomas and hyperplastic polyps often have associated GPMC.
[d]A decision to test and treat should follow shared decision-making between the patient and provider.

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syndrome (early satiety and/or fullness) have not been well studied, and available studies have yielded mixed results (27). As part of shared decision-making, the benefits and risks of antibiotic treatment should be discussed with patients with functional dyspepsia before testing for *H. pylori*.

Other groups that warrant testing and treatment for active *H. pylori* infection (Table 4) include adult household members of individuals positive for *H. pylori* by nonserological testing, patients with idiopathic (autoimmune) thrombocytopenic purpura, patients with unexplained iron deficiency, patients with a current or history of peptic ulcer disease, and those chronically taking an nonsteroidal anti-inflammatory drug or starting daily aspirin therapies (6,13).

H. pylori testing and treatment for primary and secondary prevention of gastric adenocarcinoma

Globally, gastric adenocarcinoma is the leading infection-associated cancer and the fourth leading cause of cancer-related mortality (28,29). In the CONCORD-3 analysis of global cancer survival, 5-year survival rates varied from <10% in resource-limited settings to nearly 70% in East Asia; in the United States, it was 33% (30). The near-term goal is to elevate the US 5-year survival rate to >40%–45%, using evidence-based *H. pylori* eradication (primary to tertiary prevention strategies), tailored endoscopic screening and surveillance, and new oncology therapies.

In the United States, there is marked disparity in age-standardized incidence rates of noncardia cancer that are at least double in many non-White races and ethnicities compared with non-Hispanic whites (31,32). This includes Asian, Black, Hispanic, and American Indian individuals (32,33). A study that used the California Cancer Registry found that, among individuals ≥ 50 years of age, non-White populations had a 1.8- to 13.3-fold higher incidence of noncardia gastric adenocarcinoma than non-Hispanic White individuals (34). A meta-analysis and subsequent studies indicate that immigrants moving from high- to low-incidence countries (e.g., East Asia, Mexico/Central America to North America) maintain the risk of their nation of origin (35). This is in part attributed to the higher *H. pylori* prevalence and associated virulence factors, host genetics, acculturation, and other factors (36).

Chronic *H. pylori*–related gastritis is the dominant risk factor for noncardia gastric adenocarcinoma, with an attributable risk of 75%–89% (37). The histopathologic stages, referred to as the "Correa Cascade," progress from normal gastric mucosa to chronic gastritis, to atrophic gastritis (AG), gastric intestinal metaplasia (GIM), dysplasia and, finally, gastric adenocarcinoma. AG, GIM, and dysplasia constitute gastric premalignant conditions (GPMC). The 10-year overall cumulative risk of GIM progression to gastric adenocarcinoma is estimated to be 1.6% (95% CI 1.5%–1.7%); however, in groups with high-risk GIM (see below), the risk is 2–4.5 times greater (38). Reliable, validated noninvasive tests for GPMC or gastric cancer screening and surveillance are lacking. *H. pylori* immunoglobulin G and *H. pylori* antibodies to strain-specific virulence factors (e.g., CagA and VacA) and other serologic tests to detect atrophy, including pepsinogens and gastrin, have not consistently proven reliable in North American populations.

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In a series of meta-analyses, observational studies, and clinical trials, a strategy of testing for and treating *H. pylori* has been associated with an important reduction in the incidence of, and mortality from, gastric adenocarcinoma (39–42). Most large studies have been conducted in Asia in the context of screening and surveillance programs. Two independent meta-analyses, which included RCTs and/or cohort studies, demonstrated a 46% reduction in incidence of gastric adenocarcinoma with *H. pylori* eradication (39,40). In the large population intervention on Matsu Island, Taiwan, the *H. pylori* test-and-treat strategy yielded a 53% (95% CI 30%–69%) reduction in incidence of gastric adenocarcinoma, presumed to largely have been driven by the marked reduction in *H. pylori* prevalence (64.2%–15.0%) from 2004 to 2018 (41). The strongest evidence for the benefit of *H. pylori* eradication in gastric cancer prevention is based on Asian studies demonstrating that *H. pylori* eradication treatment vs no treatment in patients with gastric cancer resection significantly reduces metachronous gastric cancer (39,42).

The utility of *H. pylori* eradication on the incidence of, and mortality from, gastric adenocarcinoma has been delineated in observational studies conducted in the United States. In the nationwide Veterans Health system, 371,813 patients with confirmed *H. pylori* eradication had a decreased risk of developing gastric adenocarcinoma with a subhazard ratio of 0.24 (95% CI 0.15–0.42) compared with those with persistent infection despite treatment (43). In a study from the Kaiser Northern California Health System, of 716,567 individuals who tested positive for *H. pylori*, those who were treated had a lower risk of gastric cancer (subdistribution HR 2.68, 95% CI 1.85–3.86) compared with those who remained untreated (subdistribution HR 6.07, 95% CI 4.20–8.76). Most of the benefit was observed 7–10 years after treatment (44), consistent with results from Asian studies.

We suggest eradication of *H. pylori* in all patients with GPMC (AG, GIM, and dysplasia) and resected early gastric cancer to reduce, respectively, the risk of GPMC progression and metachronous early gastric cancer. The greatest benefit of *H. pylori* eradication with respect to risk reduction for gastric adenocarcinoma is before the development of GPMC (i.e., at the stage of chronic gastritis). Mild to moderate AG may be reversible in some patients after successful *H. pylori* eradication. In addition to *H. pylori* eradication, endoscopic surveillance is indicated in patients with high-risk GPMC because these lesions can still progress despite successful eradication. High risk is delineated by either high-risk histology (corpus-extended GIM, incomplete GIM, and dysplasia) or specific clinical factors (family history, foreign born with immigration from a high-incidence nation, and high-risk race/ethnicity). Readers are referred to recent guidance documents for recommendations regarding endoscopic surveillance in patients with GPMC (Morgan DR et al. ACG Clinical Practice Guideline: Gastric Premalignant Conditions. Am J Gastroenterol, presubmission).

Overall, approximately 10% of patients with gastric adenocarcinoma have a positive family history. Individuals with a family history have a higher risk of developing gastric adenocarcinoma, with the magnitude of risk varying from approximately 2- to 10-fold based on observational studies (45,46). Several factors contribute to the familial aggregation of gastric adenocarcinoma, including genetic predisposition, *H. pylori* infection and strains, and shared environmental factors (e.g., diet). The recent identification of the significance of hereditary homologous recombination deficiency in combination with *H. pylori* infection in Japanese populations underscores the role of host-microbe interactions in gastric adenocarcinoma risk (47). In an elegant RCT from Korea, first-degree family members had a significant reduction in the incidence of gastric adenocarcinoma after *H. pylori* treatment (HR 0.45, 95% CI 0.21–0.94) with a greater reduction if eradication was successful (HR 0.27, 95% CI 0.10–0.70) (48).

In summary, broadly applied *H. pylori* screening and eradication for the primary prevention of gastric adenocarcinoma is not currently recommended in the general US population. However, focused testing and treatment of *H. pylori* infection is appropriate in high-risk populations (Table 4) for primary and secondary prevention.

H. pylori testing and treatment in other premalignant/malignant conditions

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a low-grade B-cell lymphoma that has been closely linked to chronic *H. pylori* gastritis (49). A recent meta-analysis of 61 uncontrolled, single-arm, observational reports (46 prospective and 15 retrospective) included 2,936 patients with early stage gastric MALT lymphoma and *H. pylori* infection. After successful eradication of *H. pylori* infection, complete remission of the gastric MALT lymphoma was reported in 75.2% (95% CI 70.5–79.9) (50). CPGs recommend eradication of *H. pylori* as the primary treatment for early stage gastric MALT lymphoma (6,51,52) despite the lack of high-quality RCTs; instead, this recommendation considers the strong potential for benefit and negligible risk of *H. pylori* eradication treatment, especially when compared with other treatments for MALT lymphoma.

With the exception of gastric fundic gland polyps, most gastric epithelial polyps arise in the setting of inflammatory conditions (e.g., *H. pylori* gastritis, autoimmune gastritis [AIG]), other insults, or—less often—polyposis syndromes. Unlike fundic gland polyps, which generally have no malignant potential, gastric hyperplastic polyps and adenomas often arise in a background of *H. pylori*–driven GPMC and can undergo malignant transformation (53,54). In patients with suspected or confirmed gastric hyperplastic polyps or adenomas, systematic biopsies (e.g., according to the Sydney protocol) are indicated with an assessment for *H. pylori* and for GPMC in the surrounding mucosa. Histologic assessment not only enables the identification and treatment of *H. pylori* infection but also facilitates endoscopic planning, including polypectomy and/or GPMC surveillance.

AIG is an immune-mediated chronic condition characterized by progressive inflammation and eventual atrophy (with or without metaplasia) of the gastric corpus as a result of autoantibody-mediated destruction of gastric parietal cells. AIG classically demonstrates antral-sparing, whereas *H. pylori*–associated atrophic gastritis, which is significantly more common than AIG, classically starts in the antrum and spreads proximally to the corpus. However, AIG and *H. pylori*–associated gastritis (with or without GPMC) may coexist. AIG is considered a premalignant condition and is associated with substantially higher risk of type I gastric neuroendocrine tumors, although these are generally indolent. AIG is also associated with an increased risk of gastric adenocarcinoma; however, recent well-performed observational studies have suggested that AIG in the absence of previous or current *H. pylori* infection carries no additional risk of gastric adenocarcinoma (55). Given the implications of

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potentially undiagnosed *H. pylori* infection for cancer risk and exacerbating nutritional deficiencies (e.g., iron deficiency), *H. pylori* testing and treatment in all patients diagnosed with AIG are recommended. This aligns with current clinical guidance on the management of AIG (56).

ERADICATING *HELICOBACTER PYLORI* INFECTION IN TREATMENT-NAIVE PATIENTS

Table 5 summarizes the recommended and suggested regimens for treatment-naive patients with *H. pylori* infection. The mechanism of action, main adverse effects, and important drug interactions for the main drugs used to treat *H. pylori* infection can be found in Supplementary Table 2 (see Supplementary Digital Content 1, http://links.lww.com/AJG/D363). Figure 1 provides an algorithm to help providers choose among the recommended and suggested treatment options. Of the recommended and suggested options for treatment-naive patients, only optimized BQT is suitable for patients with a true penicillin allergy. When optimized BQT is not an appropriate option for a patient with suspected penicillin allergy, we suggest referral to an allergist to confirm a true allergy and to consider penicillin desensitization as <1% of the population has true type 1 IgE-mediated allergy to penicillins.

Recommendation

1. In treatment-naive patients with *H. pylori* infection, optimized BQT is recommended as a first-line treatment option (strong recommendation; moderate quality evidence).

BQT typically comprises a bismuth salt (e.g., bismuth subcitrate or subsalicylate), a nitroimidazole (usually metronidazole but could also be tinidazole), tetracycline (which is preferred over doxycycline; see below), and a PPI. BQT is not approved by the US Food and Drug Administration (FDA) when prescribed separately in its 4 components. The proprietary preparation Pylera (AbbVie Pharmaceuticals, Chicago, IL) which contains bismuth subcitrate, metronidazole, and tetracycline is FDA-approved when combined with omeprazole for the treatment of *H. pylori* infection but is dispensed only as a 10-day regimen. The proprietary preparation Helidac (Prometheus Laboratories, San Diego, CA) contains bismuth subsalicylate, metronidazole, and tetracycline. It was initially approved by the FDA to be given with an H_2-receptor antagonist (H_2RA) for 14 days for the treatment of patients with *H. pylori* infection and related duodenal ulcer. We do not recommend the use of H_2RAs in treatment regimens for *H. pylori* infection and do not recommend restricting treatment to those infected patients who have peptic ulcer. We have, therefore, not further considered this preparation.

Table 5. Recommended regimens for treatment-naive patients with *H. pylori* infection

Regimen	Drugs (doses)	Dosing frequency	FDA approval	Recommendation
Optimized bismuth quadruple[a]	PPI (standard dose)[b] Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg)[d] Tetracycline (500 mg)[e] Metronidazole (500 mg)	b.i.d. q.i.d. q.i.d. t.i.d. or q.i.d.	No[c]	Strong (moderate quality of evidence)
Rifabutin triple (Talicia)[f]	Omeprazole (10 mg)[b] Amoxicillin (250 mg) Rifabutin (12.5 mg)	4 capsules t.i.d.	Yes	Conditional (low quality of evidence)
PCAB dual (Voquezna DualPak)[g]	Vonoprazan (20 mg) Amoxicillin (1,000 mg)	b.i.d. t.i.d.	Yes	Conditional (moderate quality of evidence)
PCAB triple (Voquezna TriplePak)[h]	Vonoprazan (20 mg) Clarithromycin (500 mg) Amoxicillin (1,000 mg)	b.i.d.	Yes	Conditional (moderate quality of evidence)

Recommended regimens for treatment-naive patients with *H. pylori* infection (All regimens are recommended for 14 days.).
FDA, US Food and Drug Administration; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; b.i.d., twice daily; q.i.d., 4 times daily; t.i.d., 3 times daily.
[a]Optimized bismuth quadruple therapy includes appropriately dosed PPI, bismuth, nitroimidazole (1,500–2,000 mg in divided doses), and tetracycline (not doxycycline).
[b]PPIs should be dosed 30–60 minutes before a meal.
[c]Bismuth quadruple therapy, when the components are prescribed individually, is not approved by the FDA. Two proprietary combination regimens (Pylera and Helidac) are FDA-approved. However, Pylera is only dispensed as a 10-day regimen. Helidac is dispensed as a 14-day regimen. These combination formulations should be administered with a PPI that is taken b.i.d. The original FDA approval for Helidac was with an H_2-receptor antagonist (H_2RA) and was restricted to patients with *H. pylori* infection and a duodenal ulcer. However, we do not recommend H_2RAs as part of *H. pylori* treatment regimens.
[d]Patients with a salicylate allergy should not be given bismuth subsalicylate.
[e]Doxycycline is not a recommended substitution for tetracycline.
[f]The proprietary preparation Talicia is currently the only rifabutin-containing regimen that is FDA-approved and the only one that has been evaluated as first-line treatment. Each capsule of Talicia contains omeprazole 10 mg, amoxicillin 250 mg, and rifabutin 12.5 mg. The approved dosing schedule is 4 capsules t.i.d. for 14 days. Therefore, the total daily doses of the individual components are omeprazole 120 mg (i.e., 40 mg t.i.d.), amoxicillin 3,000 mg (i.e., 1,000 mg t.i.d.), and rifabutin 150 mg (i.e., 50 mg t.i.d.).
[g]This proprietary preparation is currently the only PCAB dual regimen that is FDA-approved for the treatment of *H. pylori* infection in adults and that is available in the United States.
[h]This proprietary preparation is currently the only PCAB-clarithromycin triple regimen that is FDA-approved for the treatment of *H. pylori* infection in adults and that is available in the United States. Although it is approved for empiric first-line treatment, independent of clarithromycin resistance testing, clarithromycin-containing regimens should be reserved for patients demonstrated to have clarithromycin-sensitive strains of *H. pylori*.

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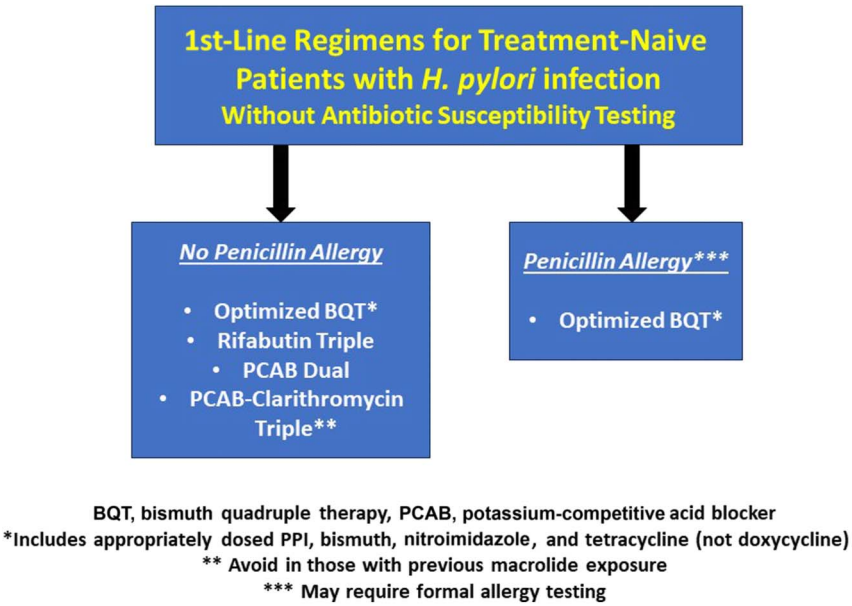
1st-Line Regimens for Treatment-Naive Patients with H. pylori infection
Without Antibiotic Susceptibility Testing
No Penicillin Allergy
• Optimized BQT*
• Rifabutin Triple
• PCAB Dual
• PCAB-Clarithromycin Triple**
Penicillin Allergy***
• Optimized BQT*
BQT, bismuth quadruple therapy, PCAB, potassium-competitive acid blocker
*Includes appropriately dosed PPI, bismuth, nitroimidazole, and tetracycline (not doxycycline)
** Avoid in those with previous macrolide exposure
*** May require formal allergy testing

Figure 1. Empiric first-line regimens for treatment-naive patients with *H. pylori* infection (no antibiotic susceptibility testing).

In a nonrandomized, single-center observational study from Brown University, Rhode Island, BQT had the highest eradication rate in routine clinical practice among treatment-naive patients (57). When given for 14 days, it eradicated *H. pylori* infection in 87% of 585 patients. Shortening the duration of BQT to 10 days reduced overall effectiveness to 77% in 135 patients. Furthermore, when doxycycline was used in place of tetracycline, effectiveness fell to 70% when given for 14 days and 67% when given for 10 days—although the numbers of patients receiving doxycycline in place of tetracycline were quite small.

BQT is recommended over PPI-clarithromycin triple therapy, which typically comprises a PPI, clarithromycin, and amoxicillin (or, less often, metronidazole in patients with penicillin allergy) given for 14 days. Eradication rates with PPI-clarithromycin triple therapy have been decreasing over time—due largely to the increasing prevalence of clarithromycin resistance related to the frequent use of macrolide antibiotics in clinical practice. In an RCT conducted in the United States and Europe, the prevalence of clarithromycin resistance was 22.2% (58). In a meta-analysis of studies on *H. pylori* isolates performed in the United States between 2011 and 2021, the pooled prevalence of clarithromycin resistance was 31.5% (59) (Figure 2a). Despite these consistent downward trends, PPI-clarithromycin triple therapy remains the most common first-line *H. pylori* treatment in the United States and elsewhere (60).

RCTs from outside North America that have compared BQT with PPI-clarithromycin triple therapy have generally shown superiority or noninferiority of the former (61–71). However, the dosages of the components of different bismuth quadruple regimens have been inconsistent among trials, as has the duration of treatment. In a network meta-analysis of a range of first-line regimens, BQT was superior to PPI-clarithromycin triple therapy among trials conducted in Western countries (72). One notable advantage of BQT over PPI-clarithromycin triple therapy is that there is no concern for possible clarithromycin resistance and no requirement or role for pretreatment antimicrobial sensitivity testing. In addition, because BQT does not contain amoxicillin, it is an appropriate option for patients with penicillin allergy. Disadvantages of BQT include the large pill burden, relatively high frequency of minor adverse events (particularly gastrointestinal), difficulties with acquisition and cost of tetracycline, and relative contraindications for tetracycline in specific patient groups (e.g., those with photosensitivity and women of childbearing potential). Although minor side effects are common, discontinuation rates because of adverse effects are low. An RCT from Taiwan reported that although >50% of treatment-naive patients with *H. pylori* infection reported at least 1 adverse effect (dark stool, fatigue, nausea, diarrhea, and dizziness all reported by >15%) with BQT, only ~5% discontinued therapy because of adverse effects (73). Similarly low rates of discontinuation because of adverse events with BQT have also been reported from Europe (74). To maximize adherence, patients should be educated on the reason it is important to treat *H. pylori* and the most frequent adverse effects that could occur with treatment.

Recommendation

2. In treatment-naive patients with *H. pylori* infection, rifabutin triple therapy is suggested as a first-line treatment option (conditional recommendation; low quality evidence)

Rifabutin triple therapy consists of a PPI, rifabutin, and amoxicillin. This regimen has traditionally been viewed as an option for treatment-experienced patients with persistent *H. pylori* infection. More recently, this combination has been evaluated in treatment-naive patients. In a meta-analysis of clinical trials that compared rifabutin triple therapy with a variety of other regimens, only a minority were randomized, and only one of the 8 that were randomized was adequately blinded (75). Furthermore, most trials were performed outside of the United States. In the United States, only 1 rifabutin-based triple regimen (Talicia; RedHill Biopharma, Raleigh, NC) is approved by the FDA for the treatment of *H. pylori* infection in adults. It is a fixed-dose combination of omeprazole, rifabutin, and amoxicillin—with

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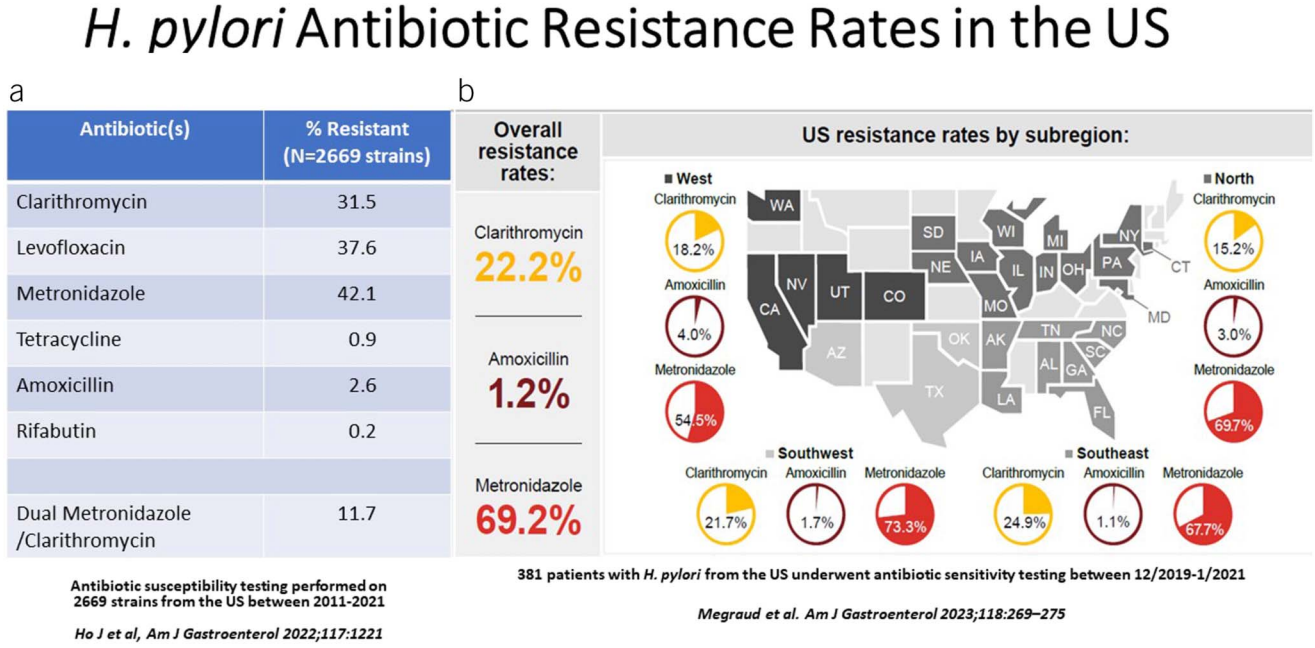

Figure 2. (**a**) Meta-analysis of antibiotic susceptibility testing performed on 2,669 *H. pylori* strains from the United States between 2011 and 2021 (58). (**b**) US regional antibiotic resistance rates among 381 patients with *H. pylori* infection (57).

total daily doses of 120 mg, 150 mg, and 3 g, respectively. In the 2 trials that led to its FDA approval, the proprietary dose of rifabutin that was used was 50 mg taken 8-hourly for 14 days; this dose may maintain the intragastric rifabutin concentration above its MIC_{90} for *H. pylori* for longer than regimens using 150 mg given once or twice daily or 300 mg given once daily (76). Furthermore, neither trial compared the rifabutin triple regimen with PPI-clarithromycin triple therapy or BQT; rather, the comparator in 1 trial was a dual combination of omeprazole 120 mg and amoxicillin 3 g in divided doses (77), whereas the other trial compared it with placebo (78). Advantages of rifabutin triple regimen are the very low rates of resistance to rifabutin and amoxicillin. Furthermore, because it does not contain clarithromycin, there is no concern for possible clarithromycin resistance and no requirement for pretreatment antimicrobial sensitivity testing. Although rifabutin has been associated with myelotoxicity, this has not been reported with total daily doses of 150 mg, which can be found in the branded rifabutin triple regimen. Randomized trials comparing rifabutin-based triple regimens with other first-line treatments, including BQT, would be of considerable interest.

Recommendation

3. In treatment-naive patients with *H. pylori* infection, dual therapy with a PCAB and amoxicillin is suggested as a first-line treatment option (conditional recommendation; moderate quality evidence).

PCABs inhibit gastric acid secretion by binding to gastric H^+/K^+ ATPase (i.e., the proton pump), but act through a different mechanism than PPIs (79). Based on comparative pharmacodynamic studies, the antisecretory effect of PCABs is more rapid, more robust, and more prolonged than that of standard doses of PPIs (80). PCABs maintain intragastric pH above 6 for longer than PPIs. At the time of writing, vonoprazan is the only PCAB approved by the FDA. Unlike most PPIs, which should be taken 30–60 minutes before a meal for optimal effect, vonoprazan can be taken in the fed or fasted state. Maintaining potent intragastric acid suppression is key for *H. pylori* eradication. This is because a high intragastric pH promotes active replication of *H. pylori*, thereby making it more susceptible to bactericidal antibiotics. A higher intragastric pH also promotes stability of acid-labile antibiotics including clarithromycin and amoxicillin, thereby increasing the intragastric concentration of these antibiotics, which may in turn influence eradication success.

Vonoprazan is the PCAB that has been the most extensively investigated worldwide and, to date, the only PCAB studied in the United States as a component of treatment regimens for *H. pylori* infection. Two vonoprazan-based regimens (discussed here and in PICO recommendation 4) were approved by the FDA in 2022 for the treatment of *H. pylori* infection in adults. These are marketed as the combination products Voquezna DualPak (vonoprazan-amoxicillin) and Voquezna TriplePak (vonoprazan-clarithromycin-amoxicillin) (Phathom Pharmaceuticals, Buffalo Grove, IL).

Only 1 RCT (81) has directly compared PCAB-amoxicillin dual therapy, comprising vonoprazan 20 mg twice daily and amoxicillin 1,000 mg 3 times daily, with PPI-clarithromycin triple therapy, comprising lansoprazole 30 mg, clarithromycin 500 mg, and amoxicillin 1,000 mg each given twice daily, with each regimen given for 14 days. This RCT was conducted in the United States and 7 European countries. Possible limitations were that almost 90% of trial participants were White and fewer than half were enrolled in the United States. Mean body mass index of study participants was around 29 kg/m^2.

In the FDA-mandated primary, noninferiority analysis in subjects with clarithromycin-sensitive strains of *H. pylori*, the vonoprazan-amoxicillin dual regimen was noninferior to the lansoprazole-clarithromycin triple regimen (eradication rates by modified ITT [mITT] analysis were 79% in each arm). In 2

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prespecified superiority analyses, vonoprazan-amoxicillin dual therapy was superior to lansoprazole-clarithromycin triple therapy among patients with clarithromycin-resistant *H. pylori* strains (70% vs 32%, $P < 0.0001$). Among the entire patient population (i.e., those with clarithromycin-sensitive and -resistant strains combined), eradication rates by mITT analysis were 77% and 69%, respectively ($P < 0.01$). Vonoprazan-amoxicillin was generally well tolerated with comparable safety profile with lansoprazole-clarithromycin triple therapy and low discontinuation rates because of adverse effects.

In China, an RCT (82) compared 2 different 10-day vonoprazan-amoxicillin regimens with a 10-day bismuth quadruple regimen that contained bismuth, clarithromycin, amoxicillin, and a PPI. Vonoprazan 20 mg twice daily was combined with amoxicillin 750 mg 4 times daily (i.e., 3 g total/day) or 1,000 mg twice daily (i.e., 2 g total/day). The regimen with the higher dose of amoxicillin was noninferior to the bismuth quadruple regimen. There were significantly fewer adverse events with the vonoprazan-amoxicillin regimens than the bismuth quadruple regimen. An additional RCT (83) from China compared a 10-day combination of vonoprazan 20 mg twice daily and amoxicillin 1,000 mg 3 times daily with a 14-day course of a bismuth-based quadruple regimen that contained amoxicillin rather than metronidazole. The vonoprazan-amoxicillin regimen was noninferior to the longer bismuth-based quadruple regimen and had significantly lower rates of adverse events including taste disturbance and diarrhea.

Advantages of the vonoprazan-amoxicillin dual regimen are its relative simplicity and low pill burden (only 2 medicines prepackaged) and, given the absence of clarithromycin, no need for pretreatment clarithromycin susceptibility testing.

High-dose dual therapy (HDDT) with a PPI has been evaluated in treatment-naive patients with *H. pylori* infection only in the context of the RCT described above, which compared *H. pylori* eradication success rates in treatment-naive patients randomized to low-dose rifabutin triple therapy vs HDDT using omeprazole 40 mg 3 times daily. Based on the modified ITT analysis, the HDDT group achieved only a 57.7% (95% CI 51.2%–64.0%) eradication success rate, with similarly poor eradication rates (64%, 95% CI 57.5%–71.2%) in the PP analysis among confirmed treatment-adherent individuals. This study also reported on cytochrome P450 2C19 (CYP2C19) metabolizer status, and nearly half of the study population were normal metabolizers.

Omeprazole, lansoprazole, and pantoprazole are extensively metabolized by CYP2C19. Several variant alleles of *CYP2C19* have been identified that translate to functional phenotypes of increased or decreased rates of metabolism and, consequently, decreased or increased PPI exposure. These are classified as ultrarapid, rapid, normal, varying stages of intermediate, likely poor, poor, and indeterminate metabolizers. CYP2C19 ultrarapid metabolizers have 2 increased function alleles *17 (*CYP2C19*17/*17*), whereas rapid metabolizers have one (*CYP2C19*1/*17*). The frequency of these alleles varies across populations of different ancestry (84). For example, the *CYP2C19*17* allele is most common in African, European, and Near Eastern populations and is estimated to be around 20%. Based on a meta-analysis, rapid/ultrarapid CYP2C19 metabolizers had a 2.5- to 4.4-fold higher likelihood of *H. pylori* eradication failure than poor metabolizers when certain PPIs were used, but there was no association between CYP2C19 metabolizer status and eradication failure when rabeprazole or esomeprazole was used (85). We do not advocate testing for *CYP2C19* genotype for the sole purpose of selecting a gastric acid suppressant in *H. pylori* treatment. However, in patients known to have the rapid or ultrarapid *CYP2C19* genotype, we suggest esomeprazole or rabeprazole as the preferred PPI. If a different PPI is used, an increase in dose is suggested. Alternatively, an approved PCAB-based regimen would be appropriate.

The most recent iteration of the Clinical Pharmacogenetics Implementation Consortium guideline for CYP2C19 and PPI dosing, published in 2021, identified that ultrarapid and rapid CYP2C19 metabolizers are at increased risk of failure of eradication with standard doses of earlier PPIs. As such, they recommend increasing the starting daily dose by 100% (ultrarapid) or 50%–100% (rapid) if omeprazole, lansoprazole, or pantoprazole is selected. Reasonable alternatives to this approach include selecting esomeprazole and rabeprazole as these bypass or are minimally metabolized by CYP2C19 or selecting a PCAB-based regimen if otherwise clinically appropriate. PCABs are not metabolized by CYP2C19. Future studies should investigate the impact and cost-effectiveness of selecting gastric acid suppression medication type/dose based on pharmacogenomic profiling.

Key concept

3. Clarithromycin- and levofloxacin-containing treatment regimens should be avoided in the absence of demonstrated macrolide and quinolone susceptibility, respectively.

Rates of resistance to clarithromycin and levofloxacin have been significantly increasing among *H. pylori* strains in many regions of the world, including the United States, and are associated with high rates of treatment failure (86). In the United States, resistance rates are currently 20%–30% for clarithromycin, and approach 40% for levofloxacin (59), which equate to predicted eradication success rates of 70% or less when used empirically in triple regimens (87). Indeed, in the face of known clarithromycin resistance, standard PPI-clarithromycin triple therapy achieves *H. pylori* eradication in fewer than a third of patients (81). Furthermore, both clarithromycin and levofloxacin are on the World Health Organization's "Watch" list of high-priority antibiotics for stewardship programs and monitoring because of their demonstrated ability to select for and promote bacterial resistance (88). It is no longer appropriate to use clarithromycin- or levofloxacin-containing treatment regimens empirically, especially in salvage therapy (see below), considering their unacceptably low rates of treatment success, the likelihood of contributing further to antimicrobial resistance among *H. pylori* and other bacterial strains, and the availability of regimens that include antibiotics with much lower resistance rates (such as amoxicillin, tetracycline, and rifabutin that are all <5%) (59). Clarithromycin- and levofloxacin-containing treatment regimens remain an important option for selected patients, especially treatment-experienced patients with confirmed persistent *H. pylori* infection with strains that are known to be susceptible to these antibiotics. That said, the numerous and potentially serious side effects of fluoroquinolones, which have resulted in an FDA black-box warning (89), should limit levofloxacin-containing regimens to patients with no other viable options and in whom a levofloxacin-sensitive strain of *H. pylori* has been identified.

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Recommendation

4. In treatment-naive patients with *H. pylori* infection and unknown clarithromycin susceptibility, PCAB-clarithromycin triple therapy is suggested over PPI-clarithromycin triple therapy (conditional recommendation; moderate quality evidence).

We advise against the use of clarithromycin in any treatment regimen unless there is evidence that a patient is infected with a clarithromycin-sensitive strain of *H. pylori*. However, we recognize that clinicians may not have access to clarithromycin susceptibility testing, particularly when managing a treatment-naive patient. In that case, the decision to include clarithromycin as part of a treatment regimen is essentially empiric.

If clarithromycin susceptibility is not known and the patient has no history of macrolide use, clarithromycin-containing triple therapy is an option if no alternative first-line therapy is available. In this scenario, evidence supports the use of a 14-day, twice-daily triple regimen that includes clarithromycin and amoxicillin along with a PCAB instead of a PPI. Three RCTs (90–92) conducted in Asia showed noninferiority or superiority of PCAB-clarithromycin triple therapy over PPI-clarithromycin triple therapy. However, these RCTs used lower doses of antibiotics than the FDA-approved vonoprazan-based regimen and administered treatment for 7 rather than 14 days.

The US and European RCT (81) discussed above included a 14-day PCAB-clarithromycin triple regimen comprising vonoprazan 20 mg, clarithromycin 500 mg, and amoxicillin 1,000 mg each given twice daily. In the primary analysis, vonoprazan-clarithromycin triple therapy was noninferior to lansoprazole-clarithromycin triple therapy in patients with clarithromycin-sensitive strains. In 2 additional prespecified superiority analyses, vonoprazan-clarithromycin triple therapy was superior to lansoprazole-clarithromycin triple therapy among patients with clarithromycin-resistant strains of *H. pylori* (eradication rates by mITT analysis were 66% and 32%, respectively; $P < 0.0001$) and among the entire study population (i.e., those with clarithromycin-sensitive and -resistant strains combined) (mITT: 81% vs 69%, $P < 0.0003$). Vonoprazan-clarithromycin triple therapy was generally well tolerated. Diarrhea (4%) and dysgeusia (4%) were the most commonly reported adverse events, with rates that were comparable with the PPI-clarithromycin triple regimen.

In a meta-analysis (93) of comparative RCTs performed in Asia, vonoprazan-based triple regimens containing clarithromycin and amoxicillin were superior to PPI-based regimens containing the same antibiotics in the same doses, both by ITT and PP analysis. A network meta-analysis (94) in which trials were subdivided by geographical region included 13 RCTs conducted in Western countries comprising 32 different treatment arms. Vonoprazan-based triple therapy showed the highest relative efficacy and had 72% probability of the being the most efficacious.

If pretreatment antibiotic sensitivity testing was widely available and routinely used, documented clarithromycin resistance would dictate against the use of any clarithromycin-based regimen—whether PCAB- or PPI-based. In a patient infected with a known clarithromycin-sensitive strain, a PCAB-based triple regimen that contained clarithromycin should be at least as effective as a similar regimen containing a PPI. However, in real-world clinical practice, providers are often confronted with patients with *H. pylori* infection in whom clarithromycin sensitivity is unknown. In such patients, if a clarithromycin-containing regimen had to be used, PCAB-clarithromycin triple therapy is suggested over PPI-clarithromycin triple therapy.

Recommendation

5. In treatment-naive patients with *H. pylori* infection, concomitant therapy is not suggested over BQT (conditional recommendation; low quality evidence).

Concomitant therapy consists of a PPI, clarithromycin, amoxicillin, and metronidazole given twice daily for durations ranging from 5 to 14 days. A meta-analysis (95) included 6 studies comprising 1,810 treatment-naive patients with *H. pylori* infection, of whom 904 were randomized to receive BQT and 906 to concomitant therapy. None of the studies was conducted in the United States. The pooled analysis showed no significant difference in eradication rates between BQT and concomitant therapy (RR 1.01, 95% CI 0.94–1.07). The overall ITT eradication rate was 87.4% (709/904) with BQT and 85.2% (772/906) with concomitant therapy. There was moderate heterogeneity among the studies ($I^2 = 44.1\%$). A subgroup analysis of 4 studies (61,96–98) at low risk of bias also yielded a small, but statistically significantly higher, eradication rate with BQT (88.2%, 682/773) than concomitant therapy (84.5%, 653/773) (RR 1.05, 95% CI 1.01–1.09, $P = 0.02$, $I^2 = 0\%$).

The most common adverse events with concomitant therapy were diarrhea and dysgeusia. Dizziness, headache, nausea, vomiting, and darkened stool were the most common adverse events with BQT. Meta-analysis found that adverse events were reported less commonly with concomitant therapy than with BQT (RR 0.90, 95% CI 0.83–0.99). This finding seemed to be driven by the results of the largest study (61).

Given the lack of evidence of superiority of concomitant therapy over BQT, the increasing rate of clarithromycin and metronidazole resistance in North America and globally, the lack of efficacy data from North America, and antibiotic stewardship considerations, concomitant therapy is not a suggested option for treatment-naive patients with *H. pylori* infection in North America. Studies to understand the comparative effectiveness of concomitant therapy in treatment-naive patients with *H. pylori* infection from the United States would be of considerable interest.

Summary of recommendations for treatment-naive patients

For treatment-naive patients with *H. pylori* infection, BQT (preferably optimized—as discussed below) for 14 days is the preferred option when the antibiotic susceptibility profile is unknown. Rifabutin triple therapy or PCAB dual therapy for 14 days are suitable alternatives as empiric therapy in patients without penicillin allergy. In patients with unknown antibiotic susceptibility and no history of macrolide exposure or penicillin allergy, PCAB-clarithromycin triple therapy for 14 days is preferable to PPI-clarithromycin triple therapy when no other obvious first-line treatment option is available.

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POST-TREATMENT TESTING FOR CURE

Key concept

4. All patients who are treated for *H. pylori* infection should undergo a test of cure with an appropriately conducted urea breath test, fecal antigen test, or biopsy-based test at least 4 weeks after completion of therapy.

Since *H. pylori* eradication rates with traditional treatment regimens have been declining in the United States over the past 2 decades, tests of cure are necessary to identify patients with persistent infection. The nonendoscopic urea breath test and fecal antigen test are both highly accurate for confirming treatment success when performed at least 4 weeks after the completion of therapy. Since PPIs can result in false-negative urea breath tests and fecal antigen tests, they should be stopped for 2 weeks before either test of cure is performed (99,100). Similar considerations will probably also apply to PCABs (such as vonoprazan), although, thus far, this has not been adequately studied (101). Standard doses of H_2RAs or antacids do not affect the accuracy of these tests. Patients should also avoid bismuth and antibiotics for at least 4 weeks before a test of cure. Because antibody levels can remain detectable for months to years after successful eradication of *H. pylori* infection, serological testing should not be used to establish post-treatment status (102).

In the rare situations when upper endoscopy is needed shortly after treating *H. pylori* infection (e.g., in patients with a large gastric ulcer or gastric MALT lymphoma), histology and/or a biopsy urease test can also be used to confirm post-treatment *H. pylori* status. Similar to urea breath testing and fecal antigen testing, the sensitivity of endoscopic tests for *H. pylori* is reduced by the recent use of PPIs (and possibly PCABs), bismuth, or antibiotics. These drugs should be withheld before endoscopic testing for the same duration as for the nonendoscopic tests. In experienced hands, *H. pylori* organisms are readily identified on histology with hematoxylin & eosin staining. In biopsies from patients with a high suspicion for *H. pylori* infection but no organisms by hematoxylin & eosin staining, such as patients who demonstrate chronic or chronic active gastritis, special stains including Giemsa, Warthin-Starry (silver), or immunohistochemistry can improve the ability to detect *H. pylori* organisms (103). A positive biopsy urease test result may be adequate to identify ongoing infection, but a negative result, without corroboration by other post-treatment testing, should not be considered definitive proof of successful *H. pylori* eradication (104).

Without testing for cure, patients with persistent infection remain at risk of potentially serious sequelae of infection including peptic ulcer, gastric adenocarcinoma, and gastric MALT lymphoma. In patients with dyspepsia and *H. pylori* infection, symptom response correlates poorly with treatment success. Thus, testing for *H. pylori* cure should be performed in all patients with dyspepsia who were treated for the infection irrespective of post-treatment symptoms. Results will inform clinicians either to consider an alternative treatment for *H. pylori* in those with persistent infection or a different dyspepsia treatment strategy in those with successful eradication. A negative post-treatment test result should be reassuring to patients and providers alike as a meta-analysis reported recurrence rates of 1% (95% CI 0.3%–3%) per year for persons in the United States who are successfully eradicated of their *H. pylori* infection. Thus, with the exception of Alaskan natives who have an *H. pylori* recurrence rate of more than 8%, recurrence of *H. pylori* infection after an evidence-based treatment regimen is quite rare in the United States (105).

An added benefit of routinely testing for cure is the ability of providers to monitor their local treatment results and to change their approach if results with certain regimens are suboptimal (e.g., if under 85%). Low eradication rates in first-line therapy should prompt consideration of testing for resistance and/or adopting a different empiric regimen.

It is encouraging that the recommendation for routine post-treatment test of cure in the 2017 ACG guideline has been accompanied by improved rates of post-treatment testing in clinical practice in the United States, from under 25% in 2005 to 60%–80% by 2019 (57,60,106). Nevertheless, these improvements should not discourage healthcare providers from further attempts at improving adherence to the recommendation for universal post-treatment testing.

ERADICATING *HELICOBACTER PYLORI* INFECTION IN TREATMENT-EXPERIENCED PATIENTS

Treatment of patients with persistent *H. pylori* infection despite 1 previous course of eradication therapy is considered "second-line" therapy. Treatment of patients with persistent *H. pylori* infection despite 2 previous courses of eradication therapy is referred to as "third-line" therapy. The umbrella term "salvage therapy" refers to any treatment provided to patients with persistent *H. pylori* infection despite initial therapy. Table 6 summarizes the recommended and suggested regimens for treatment-experienced patients with persistent *H. pylori* infection. Figures 3 and 4 are algorithms intended to assist providers to choose among the recommended and suggested treatment options. Of the recommended and suggested salvage regimens, only optimized BQT is suitable for patients with a true penicillin allergy. When optimized BQT is not an appropriate option for a patient with suspected penicillin allergy, we suggest referral to an allergist to confirm a true allergy and to consider penicillin desensitization.

Recommendation

6. In treatment-experienced patients with persistent *H. pylori* infection who have not previously received BQT, optimized BQT is suggested (conditional recommendation; very low quality of evidence).

"Optimized" BQT includes bismuth dosed as 300 mg 4 times daily at least, metronidazole 1.5–2 g daily in 3 or 4 doses, tetracycline 500 mg 4 times daily, and twice-daily standard dose PPI for 10 to (preferably) 14 days (Table 5). Optimized BQT is also available as the combination capsule of bismuth subcitrate, metronidazole, and tetracycline either as a 10-day course (Pylera; Abbvie) or a 14-day course (Helidac; Prometheus Laboratories), with a PPI dosed separately twice daily. In clinical practice, common modifications to this regimen include substitution of doxycycline for tetracycline (because of limited availability and/or cost of tetracycline), and prescribing metronidazole in doses below the recommended 1.5–2 g total daily dose. Both modifications are associated with lower *H. pylori* eradication rates and are, therefore, not recommended. In patients with persistent *H. pylori* infection following BQT that was not optimized (e.g., duration <10 days, metronidazole dosage <1.5–2 g/d, doxycycline substitution, inadequate dose of PPI), it is acceptable to repeat BQT with optimization of these elements; this represents the only

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Table 6. Recommended salvage regimens for treatment-experienced patients with persistent *H. pylori* infection

Regimen	Drugs (doses)	Dosing frequency	AST required?	Recommendation
Optimized bismuth quadruple[a]	PPI (standard dose)[b] Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg) Tetracycline (500 mg) Metronidazole (500 mg)	b.i.d. q.i.d. q.i.d. t.i.d. or q.i.d.	No	Conditional (very low quality of evidence)
Rifabutin triple	PPI (standard to double dose)[b] Amoxicillin (1,000 mg) Rifabutin (50–300 mg)[c]	b.i.d. b.i.d. or t.i.d. q.d., b.i.d., or (Talicia which contains 50 mg t.i.d.)[c]	No	Conditional (low quality of evidence)
Levofloxacin triple[d]	PPI (standard dose)[b] Levofloxacin (500 mg)[d] Amoxicillin (1,000 mg) or metronidazole[e] (500 mg)	b.i.d. q.d. b.i.d.	Yes	Conditional (low quality of evidence)
P-CAB triple (Voquezna TriplePak)[f]	Vonoprazan (20 mg) Clarithromycin (500 mg) Amoxicillin (1,000 mg)	b.i.d	Yes	No recommendation (evidence gap)
High-dose dual therapy[g]	Vonoprazan (20 mg)[h] or PPI (double dose) Amoxicillin (1,000 mg)	b.i.d. or t.i.d. t.i.d	No	No recommendation (evidence gap)

Recommended regimens for treatment-experienced patients with persistent *H. pylori* infection (All regimens are recommended for 14 days.).
AST, antibiotic sensitivity testing; FDA, US Food and Drug Administration; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; b.i.d., twice daily; q.d., once daily; q.i.d., 4 times daily; t.i.d., 3 times daily.
There are no FDA-approved regimens for the treatment of persistent *H. pylori* infection.
[a]Optimized bismuth quadruple therapy includes appropriately dosed PPI, bismuth, nitroimidazole (1,500–2,000 mg in divided doses), and tetracycline. Patients with a salicylate allergy should not be given bismuth subsalicylate. Doxycycline is not a recommended substitution for tetracycline because of higher rates of failure. The proprietary combination regimen Pylera is acceptable but is only available as a 10-day regimen. Helidac dosed with a twice-daily PPI for 14 days is an appropriate selection.
[b]PPIs should be dosed 30–60 minutes before a meal.
[c]The optimal dosing strategy for rifabutin in rifabutin triple salvage therapy is unclear. Rifabutin 50 mg tablets are not commercially available. Although Talicia provides rifabutin as 50 mg t.i.d., it has not been evaluated as salvage therapy. If prescribing the drugs separately, we suggest rifabutin 150 mg b.i.d. or 300 mg q.d. when used as part of salvage therapy.
[d]Levofloxacin has a black-box warning because of risk of tendonitis and tendon rupture. This regimen is only suggested in treatment-experienced patients with persistent *H. pylori* infection that is confirmed to be levofloxacin-sensitive.
[e]Metronidazole should be used in place of amoxicillin for levofloxacin triple therapy in patients with true penicillin allergy.
[f]This proprietary preparation is currently FDA-approved for the treatment of *H. pylori* infection in adults but has not been evaluated as a salvage regimen. Therefore, a recommendation cannot be made for or against its use in treatment-experienced patients with persistent *H. pylori* infection. This regimen should not be used in individuals with previous macrolide exposure, nor should it be used in individuals without demonstrated clarithromycin-sensitive *H. pylori* strains.
[g]High-dose dual therapy consists of high-potency gastric acid suppression therapy (i.e., high-dose PPI or PCAB) and high-dose amoxicillin. There is vast heterogeneity in the literature regarding the dose and choice of PPI. Although an attractive option because of its simplicity and alignment with antimicrobial stewardship, there is insufficient evidence from North America to recommend this regimen for salvage treatment.
[h]Voquezna DualPak, which contains vonoprazan 20 mg b.i.d. and amoxicillin 1,000 mg t.i.d., is a proprietary preparation that is FDA-approved for the treatment of *H. pylori* infection in adults, but it has not been evaluated as a salvage regimen. Therefore, a recommendation cannot be made for or against its use in treatment-experienced patients with persistent *H. pylori* infection.

exception to the adage to not repeat a previously failed regimen when treating persistent *H. pylori* infection.

Two systematic reviews published in 2018 and 2020 identified RCTs of second-line *H. pylori* eradication treatment and performed network meta-analyses to evaluate their comparative effectiveness (107,108). Most studies were from Asian-Pacific countries. The larger of the 2 network meta-analyses included 54 RCTs with 8,752 participants and compared 16 second-line *H. pylori* eradication regimens with 7-day BQT as the study-defined reference regimen (107). The other included 26 RCTs with 3,628 participants and compared 7 second-line eradication regimens with 7-day triple therapy as the study-defined reference regimen (108). Secondary analyses included comparisons to BQT for 10 or 14 days. Moreover, although most BQT regimens included bismuth, metronidazole, tetracycline, and a twice-daily PPI, some BQT arms included alternative antimicrobials as substitutes for either tetracycline or metronidazole (e.g., furazolidone, which is not available in the United States, amoxicillin, or levofloxacin). Differences in dosages, PPIs, and populations (e.g., according to geography, gastroduodenal pathology, previous eradication treatment, and *H. pylori* antibiotic resistance profiles) also contributed to significant heterogeneity across studies.

Based on pooled eradication rates from RCTs conducted in patients with persistent *H. pylori* infection despite 1 previous course of therapy, BQT for 10–14 days achieved successful *H. pylori* eradication in 78.8% (vs 67.8% mean eradication success rate for BQT for 7 days) (107). These pooled estimates were

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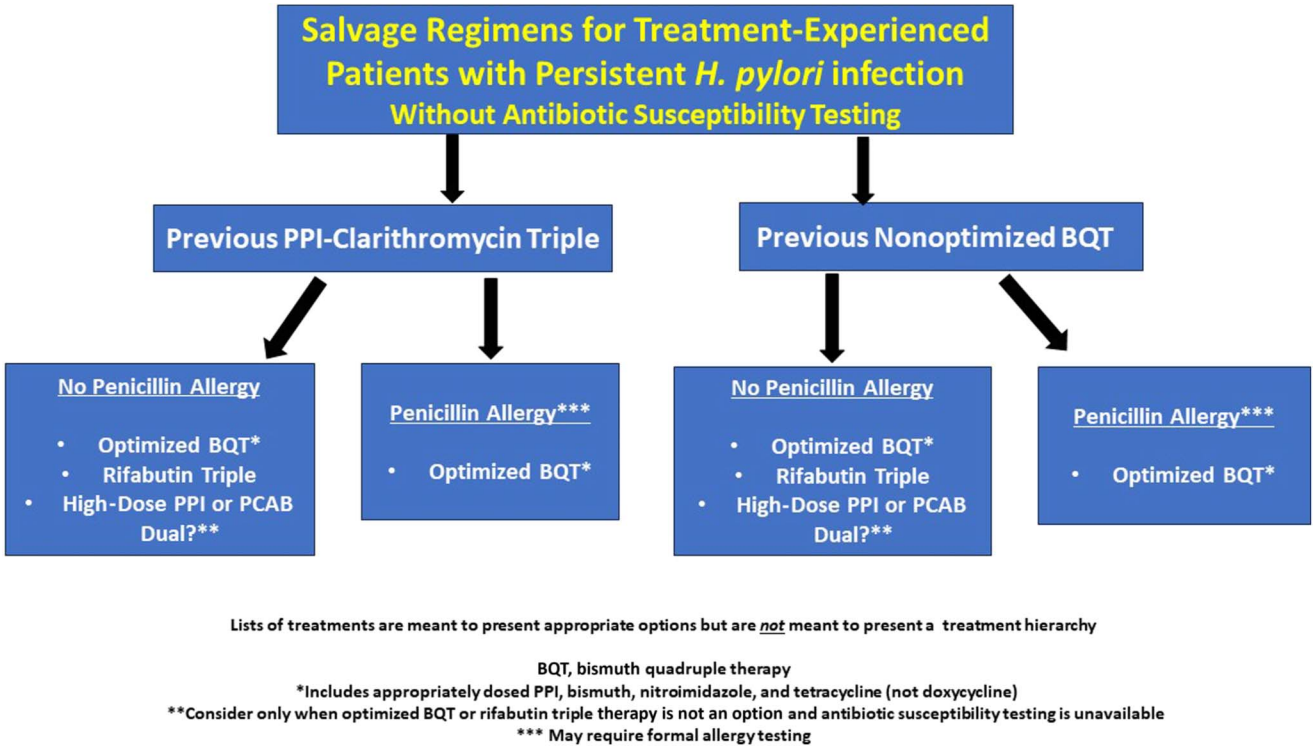
Salvage Regimens for Treatment-Experienced Patients with Persistent H. pylori infection Without Antibiotic Susceptibility Testing
Previous PPI-Clarithromycin Triple
Previous Nonoptimized BQT
No Penicillin Allergy
Optimized BQT*
Rifabutin Triple
High-Dose PPI or PCAB Dual?**
Penicillin Allergy***
Optimized BQT*
No Penicillin Allergy
Optimized BQT*
Rifabutin Triple
High-Dose PPI or PCAB Dual?**
Penicillin Allergy***
Optimized BQT*
Lists of treatments are meant to present appropriate options but are not meant to present a treatment hierarchy
BQT, bismuth quadruple therapy
*Includes appropriately dosed PPI, bismuth, nitroimidazole, and tetracycline (not doxycycline)
**Consider only when optimized BQT or rifabutin triple therapy is not an option and antibiotic susceptibility testing is unavailable
*** May require formal allergy testing

Figure 3. Empiric salvage regimens for treatment-experienced patients with persistent *H. pylori* infection (no antibiotic susceptibility testing).

predominantly driven by data from Asian-Pacific countries and among individuals who most often had failed clarithromycin or nonclarithromycin triple therapy as their first treatment regimen. Far fewer of the studies included individuals who had initially failed treatment with BQT. The only RCT from the United States enrolled 48 subjects, of whom only 28 were treated with second-line BQT therapy; BQT achieved 71% (95% CI 54%–88%) and 80% (95% CI 64%–96%) eradication rates in ITT and PP analyses, respectively (109). Most individuals in the trial had failed ranitidine bismuth citrate, metronidazole, and tetracycline (n = 27), whereas only 8 had failed previous PPI-clarithromycin triple therapy or BQT. For the BQT regimen used as second-line therapy, the dosages of metronidazole (250 mg 4 times daily) and tetracycline (250 mg 4 times daily) were lower than recommended for optimized BQT, lansoprazole 30 mg was given 4 times daily rather than twice daily, and the bismuth dose was not specified. This study also had high risk of bias because of deviation from the intervention because patients already randomized to PPI-clarithromycin triple therapy were given BQT instead if they had penicillin allergy.

In a systematic review of European studies evaluating *H. pylori* salvage regimens in patients who had most often failed PPI-clarithromycin triple therapy, component BQT achieved ITT and PP eradication rates of 75.6% (95% CI 66.1%–85.1%) and 75.7% (95% CI 65.4%–86%) (based on data from 78 individuals), respectively, as second-line therapy and 64.1% (95% CI 58.1%–70.2%) and 93.3% (95% CI 90.1%–96.6%) (based on data from 240 individuals), respectively, as third-line therapy (110). Notably, BQT as a combination product achieved significantly higher eradication success rates as second-line (89.2%, 95% CI 87.4%–91.0% [ITT] and 92.2%, 95% CI 90.4%–93.9% [PP]; based on data from 1,120 individuals) and third-line (83.6%, 95% CI 79.6%–87.6% [ITT] and 86%, 95% CI 81.5%–90.4% [PP]; based on data from 330 individuals) therapies vs component BQT therapy (second-line therapy, 75.6% [ITT] and 75.7% [PP] based on 78 individuals; third-line therapy, 64.1% [95% CI 58.1%–70.2%] [ITT] and 93.3% [95% CI 90.1%–96.6%] [PP], based on 240 individuals) (110). Another study pooled eradication rates for salvage regimens used as third-line therapy (details of previous treatments not consistently provided) in RCTs and observational studies and reported that component BQT therapy achieved an ITT eradication rate of 69.2% and PP eradication rate of 72.1%, whereas combination pill-BQT achieved an ITT eradication rate of 88.9% and a PP eradication rate of 90.9% (95% CI not provided for estimates) (111). Finally, a multicenter, open-label parallel-group RCT conducted in 8 hospitals across Taiwan enrolled 560 patients with persistent *H. pylori* infection despite treatment with PPI-clarithromycin triple therapy. The 10-day BQT arm (with esomeprazole 40 mg twice daily) achieved 88% (95% CI 84%–91%) (ITT) and 93% (95% CI 90%–96%) (PP) success rates, which were similar to levofloxacin-based sequential therapy (88%, 95% CI 84%–92% [ITT]/90%, 95% CI 87%–94% [PP]) (112).

Based on these data, we suggest optimized BQT for 14 days in patients with persistent *H. pylori* infection who have not previously received optimized BQT. BQT as a combination product may be more effective than providing its components separately, possibly related to improved patient adherence. The quality of evidence was downgraded to "very low" because of indirectness, study design, large heterogeneity of pooled studies, and because the pooled eradication rates were based on secondary analysis of existing data and not direct trial comparisons.

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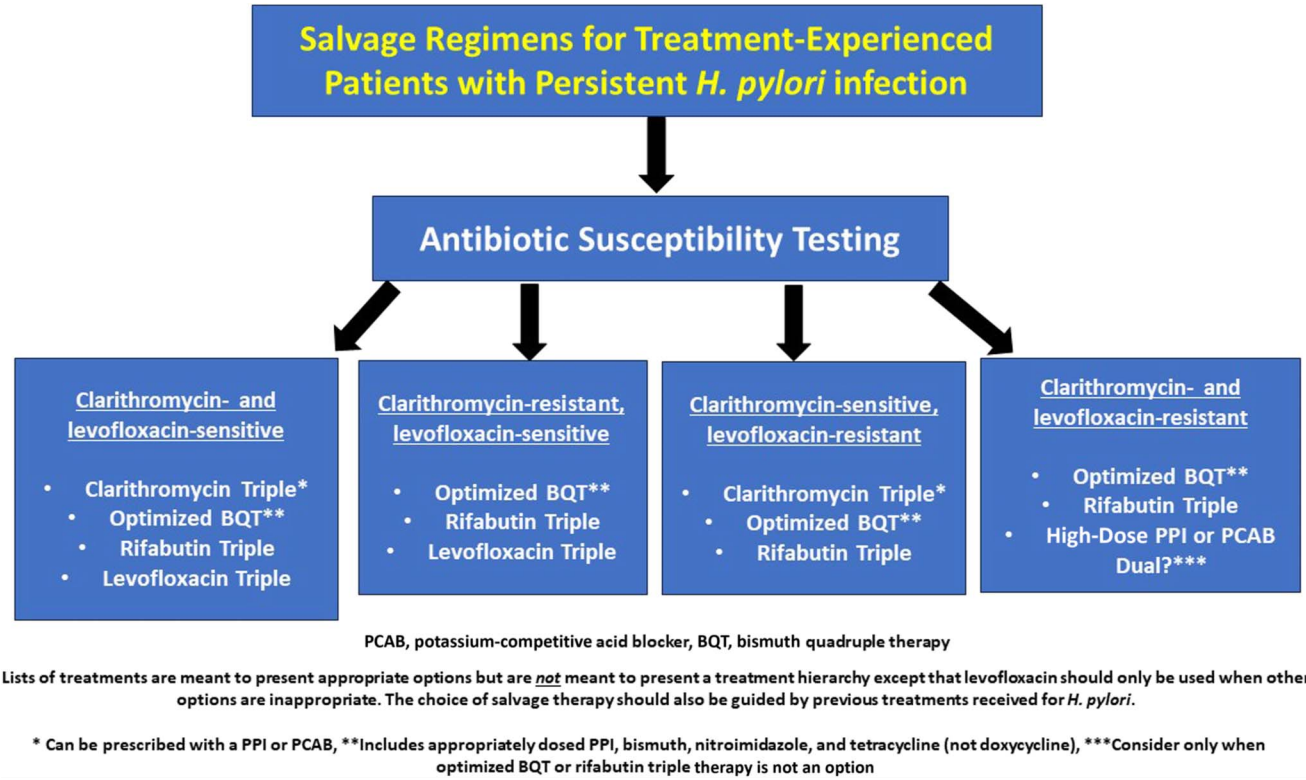
Salvage Regimens for Treatment-Experienced Patients with Persistent H. pylori infection
Antibiotic Susceptibility Testing
Clarithromycin- and levofloxacin-sensitive
Clarithromycin Triple*
Optimized BQT**
Rifabutin Triple
Levofloxacin Triple
Clarithromycin-resistant, levofloxacin-sensitive
Optimized BQT**
Rifabutin Triple
Levofloxacin Triple
Clarithromycin-sensitive, levofloxacin-resistant
Clarithromycin Triple*
Optimized BQT**
Rifabutin Triple
Clarithromycin- and levofloxacin-resistant
Optimized BQT**
Rifabutin Triple
High-Dose PPI or PCAB Dual?***
PCAB, potassium-competitive acid blocker, BQT, bismuth quadruple therapy
Lists of treatments are meant to present appropriate options but are not meant to present a treatment hierarchy except that levofloxacin should only be used when other options are inappropriate. The choice of salvage therapy should also be guided by previous treatments received for H. pylori.
* Can be prescribed with a PPI or PCAB, **Includes appropriately dosed PPI, bismuth, nitroimidazole, and tetracycline (not doxycycline), ***Consider only when optimized BQT or rifabutin triple therapy is not an option

Figure 4. Antibiotic susceptibility testing guided salvage regimens for treatment-experienced patients with persistent *H. pylori* infection.

Recommendation

7. In treatment-experienced patients with persistent *H. pylori* infection who have previously received PPI-clarithromycin triple therapy, optimized BQT is suggested (conditional recommendation; low quality of evidence).

In network meta-analyses, all included studies that evaluated triple therapy as second-line treatment used nonclarithromycin triple regimens (predominantly quinolone-based) except for the 1 small US study (107–109). In 1 study, 48 individuals with persistent *H. pylori* infection despite 1 previous course of eradication therapy were randomized to either 14-day BQT (lansoprazole 30 mg, bismuth 2 tablets [dose not provided], metronidazole 250 mg, and tetracycline 250 mg, all given 4 times daily) or PPI-clarithromycin triple therapy (lansoprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg, all given twice daily) (109). There was no statistically significant difference in eradication success rates between PPI-clarithromycin triple therapy and BQT on ITT (75% [95% CI 56%–94%] vs 71% [95% CI 54%–88%]) or PP (82% [95% CI 64%–100%] vs 80% [96% CI 64%–96%]) analyses (109). However, as already noted, this study used low metronidazole and tetracycline doses for BQT and had high risk of bias because of deviation from the protocol intervention. Our independent comprehensive literature search identified this RCT as the only direct evidence comparing PPI-clarithromycin triple therapy with BQT as second-line therapy.

Thus, in treatment-experienced patients with persistent infection who have previously received PPI-clarithromycin triple therapy, salvage treatment with optimized BQT is suggested. Despite the paucity of evidence and practical challenges with BQT, including tetracycline cost and frequent side effects, the guideline committee still prefers optimized BQT over clarithromycin- or levofloxacin-containing salvage regimens, unless susceptibility to these antibiotics is demonstrated. The rising rates of resistance of *H. pylori* to clarithromycin and levofloxacin in North America, and the United States in particular, as well as the black-box warning for levofloxacin strongly influenced the guideline committee's recommendation. As already noted, a basic core principle for treating *H. pylori* infection is to avoid clarithromycin and levofloxacin in individuals who have had any exposure to, respectively, macrolides or fluoroquinolones. However, US nationwide claims-based data demonstrated that, among individuals who required a second-line *H. pylori* treatment, most were prescribed the same regimen, with more than 50% receiving a repeat course of PPI-clarithromycin triple therapy despite the lack of antibiotic susceptibility testing in the interval (60). Clearly, further education efforts and changes in practice are needed to improve the quality of care in patients with *H. pylori* infection.

Recommendation

8. In treatment-experienced patients with persistent *H. pylori* infection who have received BQT, rifabutin triple therapy is suggested (conditional recommendation; low quality of evidence).

Similar to treatment-naive patients, when used in treatment-experienced patients with persistent *H. pylori* infection, rifabutin triple therapy consists of a PPI, rifabutin, and amoxicillin. The literature search identified only 1 head-to-head comparison of 14-day rifabutin triple therapy and 14-day BQT for treatment-

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experienced patients with persistent *H. pylori* infection. This was an open-label, noninferiority RCT from China that included 364 patients who had failed at least 2 previous *H. pylori* therapies (8). Notably, no patients had previously received BQT because tetracycline is not widely available in China. Rifabutin triple therapy comprised rifabutin 150 mg, amoxicillin 1 g, and esomeprazole 20 mg, each given twice daily and achieved ITT, mITT, and PP eradication rates of 89.0% (95% CI 83.6%–92.8%), 93.6% (95% CI 89.0%–96.4%), and 94.0% (95% CI 89.3%–96.7%), respectively. These were noninferior to BQT, which comprised bismuth 660 mg twice daily, metronidazole 400 mg 4 times daily, tetracycline 500 mg 4 times daily, and esomeprazole 20 mg twice daily and achieved ITT, mITT, and PP eradication rates of 89.6% (95% CI 84.3%–93.2%), 93.7% (95% CI 89.0%–96.4%), and 95.3% (95% CI 90.7%–97.7%), respectively. The rifabutin triple therapy group had significantly lower rates of total adverse events (26.4% vs 54.4%, $P < 0.001$) and moderate-severe adverse events (14.3% vs 28.6%, $P < 0.001$) than the BQT group. Compliance was also higher for rifabutin triple therapy than BQT (96% vs 85%). Antibiotic resistance in this study group with at least 2 previous failed therapies was 90%–97% for clarithromycin, 85%–86% for levofloxacin, and 95% for metronidazole, but only 9%–11% for amoxicillin, 0.7% for tetracycline, and 0% for rifabutin. *In vitro* metronidazole resistance was not associated with eradication failure in patients receiving optimized BQT.

The only other RCT comparing rifabutin triple therapy with BQT as salvage therapy gave both for 7 days. All other data regarding 10- or 14-day rifabutin triple therapy in treatment-experienced patients with persistent infection are from observational studies without direct comparisons to optimized BQT. Based on a systematic review that included European studies only, the pooled ITT and PP eradication rates of rifabutin triple therapy were 72.2% (95% CI 68%–77%) (ITT) and 77% (95% CI 72%–80%) (PP) (411 individuals) as second line, 79.6% (95% CI 75.7%–83.5%) (ITT) and 85.1% (95% CI 81.6%–88.7%) (PP) (412 individuals) as third line, and 76.8% (95% CI 71.2%–82.4%) (ITT) and 82.2% (76.9%–87.4%) (PP) (216 individuals) for more than third line (110), which were similar to pooled eradication rates reported in another systematic review (111); notably, these pooled eradication rates encompassed rifabutin triple therapy for 7–14 days, without distinction between the 2 durations. As with other *H. pylori* treatment regimens, 10- or, preferably, 14-day duration should always be selected over 7 days.

Generic rifabutin is available as a 150-mg tablet, and there is insufficient evidence to inform what the optimal dose of rifabutin is for *H. pylori* treatment (e.g., 50 mg 3 times daily, 150 mg once daily, 150 mg twice daily or 300 mg once daily). The few studies evaluating rifabutin 150 mg once daily have demonstrated lower eradication rates than 300 mg once daily or 150 mg twice daily. However, higher doses of rifabutin are associated with a greater risk of transient myelosuppression, which seems to be dose-dependent. Although FDA-approved for the treatment of *H. pylori* infection in adults, the commercially available rifabutin triple capsule (Talicia; RedHill Biopharma) has only been evaluated in treatment-naive patients. As noted above, pharmacokinetic modeling demonstrated that rifabutin 50 mg 3 times daily (76) produces a significantly longer duration of time with an intragastric rifabutin concentration above its MIC_{90} for *H. pylori* (22.3 ± 1.1 hours) than 150 mg once daily (8.3 ± 1.7 hours), 150 mg twice daily (16.3 ± 2.3 hours), and 300 mg once daily (8.5 ± 1.9 hours), while achieving the lowest mean maximal plasma concentration. Assuming that intragastric rifabutin concentrations correlate with eradication success, and that plasma concentration may correlate with myelotoxicity, we suggest 50 mg 3 times daily or, if Talicia is unavailable, 150 mg twice daily when using rifabutin triple therapy as a salvage regimen.

Based on the available evidence and expert consensus, we suggest rifabutin triple therapy for 14 days in treatment-experienced patients with persistent *H. pylori* infection who have previously received optimized BQT. This statement takes into consideration the World Health Organization "watchlist" and reserved status of rifabutin. Of note, no studies have yet evaluated *H. pylori* eradication rates when a PCAB is substituted for a PPI in rifabutin triple therapy.

Key concept

5. In treatment-experienced patients with persistent *H. pylori* infection that is confirmed to be clarithromycin-sensitive, PPI- or PCAB-clarithromycin triple therapy is suggested.

As the recommendations of this guideline for the first-line treatment of *H. pylori* infection are incorporated into clinical practice, a larger proportion of treatment-experienced patients with persistent *H. pylori* infection will have previously been treated with BQT, rifabutin triple therapy, or vonoprazan-amoxicillin dual therapy. If, related to previous use, high cost, or a lack of availability, treatment regimens containing clarithromycin or levofloxacin need to be considered, antibiotic susceptibility testing (see Key concept 6) should be performed. Here, we discuss clarithromycin triple therapy as salvage therapy, whereas quinolone-based salvage therapy is discussed below.

There are no RCTs or robust observational data from North America that evaluate clarithromycin triple therapy as salvage therapy after BQT, rifabutin triple therapy, or vonoprazan-amoxicillin dual therapy. Thus, the guideline panel used expert consensus to suggest PPI- or PCAB-clarithromycin triple salvage therapy in patients with persistent *H. pylori* infection confirmed to be sensitive to clarithromycin by antibiotic susceptibility testing. As noted above, the bactericidal activity of clarithromycin and amoxicillin on susceptible *H. pylori* strains is critically dependent on achieving and maintaining adequate gastric acid suppression (intragastric pH >6). Accordingly, every effort should be made to optimize other aspects of treatment known to influence treatment success (113), particularly when clarithromycin triple therapy is being considered as a salvage regimen; this includes attention to patient adherence and optimization of gastric acid suppression. The only clinical scenario in which clarithromycin triple therapy could be repeated in a patient who previously failed PPI-clarithromycin triple as initial therapy is if *H. pylori* sensitivity to clarithromycin and amoxicillin has been demonstrated on antibiotic susceptibility testing, and there is opportunity for optimization of gastric acid suppression. For instance, if a patient was adherent to but failed PPI-clarithromycin triple therapy, the guideline panel suggests using esomeprazole or rabeprazole or a PCAB in the salvage regimen if not already used in the previous regimen. We reiterate that these suggestions are based on expert consensus and are, therefore, subject to revision. Comparative studies, as well as surveillance data from prospectively maintained registries, regarding the effectiveness of the above approach in a North American population would be highly informative.

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Recommendation

9. In treatment-experienced patients with persistent *H. pylori* infection who have not previously received optimized BQT, optimized BQT is suggested over quinolone-based therapy (conditional recommendation; low quality of evidence).

Recommendation

10. In treatment-experienced patients with persistent *H. pylori* infection, levofloxacin triple therapy is suggested in patients with known levofloxacin-sensitive *H. pylori* strains and when optimized bismuth quadruple or rifabutin triple therapies have previously been used or are unavailable (conditional recommendation, low quality of evidence).

Quinolone triple therapy, which typically consists of a PPI, levofloxacin or moxifloxacin, and amoxicillin or a nitroimidazole, has long been used as salvage therapy for treatment-experienced patients with persistent *H. pylori* infection. Several randomized and nonrandomized trials have compared quinolone-based therapy vs BQT in treatment-experienced patients with persistent infection, with heterogeneity across studies related to treatment regimen components and their dosing/frequency, treatment duration (i.e., 7, 10, or 14 days), population, geography (e.g., Korea, Brazil, Vietnam, China, Italy, or Greece), type of previous failed *H. pylori* treatment regimens, and local antibiotic resistance rates. Most previous studies have evaluated quinolone triple therapy (114), with very few studies evaluating quinolone quadruple therapy vs BQT (115,116). Most quinolone triple regimens evaluated in these studies included a PPI twice daily, levofloxacin/moxifloxacin 400–500 mg daily in one or divided doses, and amoxicillin or a nitroimidazole, usually twice daily. However, a few studies included azithromycin or furazolidone; there was also heterogeneity in the components comprising quinolone-based quadruple therapy. Considering this heterogeneity, the pooled eradication rate of quinolone triple therapy for 10–14 days in patients with persistent infection despite 1 previous course of eradication therapy (second-line salvage therapy) was 79%. The network meta-analysis described above (107) demonstrated no significant difference in success rates between quinolone triple therapy and BQT for 10–14 days (107). However, there was statistically significant inconsistency in the comparisons. In a meta-analysis, the pooled ITT eradication rate of levofloxacin triple therapy twice daily as second-line treatment was 74.5% (95% CI 70.9%–77.8%), although this comprised regimens of varying duration (7–14 days), selection and dose of PPI (pantoprazole 40 mg twice daily to rabeprazole 20 mg 3 times daily), amoxicillin/levofloxacin dosing, and levofloxacin resistance (114). The 10- to 14-day regimens produced success rates ranging from 70.6% to 100% in individual studies. High-dose ($>$500 mg) and lower-dose ($\leq$500 mg) levofloxacin led to similar treatment outcomes (114). In a meta-analysis that evaluated only European trials, the pooled eradication rate for levofloxacin triple therapy, albeit with varying regimen components and duration, as second-line salvage therapy was 69.1% (95% CI 65.4%–72.9%) for ITT and 75.6% (95% CI 71.9–79.2) for PP (110). Levofloxacin triple therapy achieved higher eradication rates when 14- rather than 10-day duration was used (87.1% vs 72.2%; $P = 0.003$). A multicenter RCT compared quinolone sequential therapy (esomeprazole 40 mg + amoxicillin 1 g, each given twice daily for 7 days, followed by esomeprazole 40 mg, metronidazole 500 mg, and levofloxacin 250 mg, each given twice daily for 7 days) vs BQT (bismuth 300 mg, tetracycline 500 mg, and metronidazole 500 mg given 4 times daily with esomeprazole 40 mg given twice daily) for 10 days in 560 Taiwanese patients who had persistent *H. pylori* infection despite previous treatment with clarithromycin-based therapy (112). They reported no difference in eradication rates between the 2 regimens based on ITT (88% vs 88%, $P = 0.90$) and PP (90% vs 93%) analyses, although the quinolone-based regimen had lower patient-reported side effects (48% vs 77%). In patients who had failed 2 previous attempts at eradication therapy or third-line salvage treatment, the pooled eradication rate of levofloxacin triple therapy ranged from 55.7% (111) to 84.1% (110).

It is well-established that *H. pylori* resistance to levofloxacin is associated with significantly higher rates of failure when a levofloxacin-containing regimen is used, both in treatment-naive and treatment-experienced patients. In a meta-analysis, the pooled eradication rate with levofloxacin triple therapy was 81.1% (95% CI 67.6%–89.9%) in individuals with levofloxacin-susceptible strains vs 36.3% (95% CI 25.2%–49.2%) in those with resistant strains (114). If the prevalence of levofloxacin resistance is 20%, 30%, 40%, or $>$50%, the predicted efficacy of levofloxacin triple therapy is approximately 72%, 68%, 63%, and $<$59%, respectively (114).

Based on the available data, quinolone-based therapy and optimized BQT achieve similar eradication rates when used for second-line treatment of *H. pylori* infection. However, considering the ever-increasing rates of *H. pylori* resistance to levofloxacin globally, including the United States, and its negative impact on eradication success, as well as the black-box warning for fluoroquinolones because of tendonitis and tendon rupture, we suggest optimized BQT over quinolone-based therapy in patients who have not previously received optimized BQT. In treatment-experienced patients with persistent *H. pylori* infection who have demonstrated *H. pylori* susceptibility to levofloxacin, levofloxacin triple therapy for 14 days is suggested when BQT or a rifabutin triple regimen has previously been used or is unavailable.

Recommendation

11. In treatment-experienced patients with persistent *H. pylori* infection, there is insufficient evidence from North America to recommend high-dose PPI or PCAB dual therapy (no recommendation; evidence gap).

HDDT consists of potent gastric acid suppression therapy (e.g., high-dose PPI or PCAB) and high-dose amoxicillin, preferably for 14 days. In theory, this combination is attractive from an antibiotic stewardship standpoint because it uses only 1 antibiotic and *H. pylori* resistance to amoxicillin is low in most populations. However, the data regarding its efficacy as a salvage regimen are very limited, and there are no RCTs from North America. The only study from a Western population is a small noninferiority RCT from Germany published in 2003 (117). In this study, 84 patients with at least 1 previous *H. pylori* treatment failure and confirmed persistent infection with clarithromycin- and metronidazole-resistant (but amoxicillin-susceptible) *H. pylori*, were randomized to HDDT given as omeprazole 40 mg and amoxicillin 750 mg, each administered 4 times daily, or

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BQT consisting of bismuth citrate 107 mg, metronidazole 500 mg, and tetracycline 500 mg each given 4 times daily along with omeprazole 20 mg twice daily for 14 days. Eradication rate with HDDT was 75.6% (ITT) and 83.8% (PP) and was noninferior to BQT (81.4% ITT, 92.1% PP). In the crossover arm, 3 of 3 patients who failed HDDT had success with BQT, whereas 1 of 2 patients who failed BQT had success with HDDT.

The literature search identified other RCTs that used HDDT in treatment-experienced patients with persistent infection, but the reference groups for comparison were 7-day rifabutin triple or 7-day nonclarithromycin triple therapy (118). One noninferiority RCT reported on the efficacy of HDDT (esomeprazole 40 mg and amoxicillin 1 g, each given 3 times daily for 14 days) compared with BQT with furazolidone instead of metronidazole (esomeprazole 40 mg twice daily with bismuth 220 mg, furazolidone 100 mg, tetracycline 500 mg, each given twice daily for 14 days) (119). This study included 658 Chinese patients (mean body mass index 22.5–22.9) who had failed at least 1 *H. pylori* treatment and concluded that HDDT was noninferior to BQT. Success rates based on ITT, mITT, and PP analyses were 75.4%, 81%, and 81.3%, respectively, for HDDT and 78.1%, 84.2%, and 85.1%, respectively, for furazolidone BQT. Adverse events were lower with HDDT than furazolidone BQT (11% vs 26%), but compliance was similar (119). The literature search identified no studies of PCAB-based HDDT compared with BQT in treatment-experienced patients with persistent infection.

Thus, there is insufficient evidence from North America to recommend for or against PPI or PCAB HDDT in treatment-experienced patients with persistent *H. pylori* infection. The efficacy of HDDT as salvage therapy in diverse US populations represents a major knowledge gap and warrants dedicated investigation with particular attention to the appropriate selection of patients, the choice of and dosing schedule of gastric acid suppression therapy, and dosing schedule for amoxicillin. Although we do not recommend HDDT as a routine salvage regimen in patients with persistent *H. pylori* infection, it may be considered in selected scenarios such as patients in whom optimized BQT or rifabutin triple therapy is not an option; antibiotic susceptibility testing is unavailable or does not yield usable results; or in patients with a strain of *H. pylori* that is sensitive only to amoxicillin.

Summary of recommendations for treatment-experienced patients

In summary, optimized BQT for 14 days is the preferred option for treatment-experienced patients with persistent *H. pylori* infection who have not been treated with optimized BQT previously and for whom the *H. pylori* resistance profile is unknown. If bismuth and/or tetracycline is unavailable, or in individuals previously treated with optimized BQT, rifabutin triple therapy for 14 days is a suitable alternative. For patients with persistent infection after optimized BQT and/or rifabutin triple therapy, or in whom rifabutin therapy cannot be used (e.g., because of true penicillin allergy), antibiotic susceptibility testing is recommended to guide further therapy with salvage regimens containing clarithromycin or levofloxacin. In patients who are known to be infected with clarithromycin-sensitive *H. pylori* and who have not received clarithromycin triple therapy with recommended doses of clarithromycin and amoxicillin, optimized PPI- or PCAB-clarithromycin triple therapy for 14 days is a viable option. In individuals who have not previously received a levofloxacin-containing regimen and who are known to be infected with a levofloxacin-sensitive strain of *H. pylori*, levofloxacin triple therapy for 14 days is a viable option, acknowledging and considering the safety concerns and black-box warning. There is insufficient evidence to offer a recommendation for HDDT for treatment-experienced patients with persistent infection in a North American population.

ANTIBIOTIC SUSCEPTIBILITY TESTING

Key concept

6. *H. pylori* antibiotic susceptibility tests using either phenotypic (culture-based) or molecular methods (polymerase chain reaction [PCR] or next-generation sequencing [NGS]) are becoming increasingly available in the United States. The incremental benefit of selecting an eradication regimen "tailored" to the antibiotic susceptibility profile compared with empiric selection of eradication therapy remains to be adequately defined and studied—for both treatment-naive and treatment-experienced patients. Based on expert consensus, we advise using antibiotic susceptibility testing whenever the choice of therapy remains unclear after taking into consideration any previous treatments for *H. pylori* infection, past antibiotic exposure more generally, and whether there is a documented history of penicillin allergy.

A natural consequence of the formal classification of *H. pylori* infection as an infectious disease is that treatment selection should be guided by the likely or actual antibiotic susceptibility of the organism in an individual patient. This tailored approach, contrasting with the empiric approach that has been followed in the past, has the potential to improve success rates and to reduce the occurrence and impact of inappropriate antibiotic prescription (120).

Antibiotic susceptibility in *H. pylori* can be evaluated phenotypically, through bacterial culture and measuring growth inhibition by specific antibiotic exposure, or genetically through molecular analysis. Culture can be performed in several ways, with no universally accepted international gold-standard (121,122). Although culture-based *H. pylori* susceptibility testing is available in the United States, it is not widely used as a consequence of operational/workflow complexities, low rates of successful culture, and uncertainty over the incremental value of culture-based susceptibility results in treatment selection (123).

Molecular testing for genetic variants that confer resistance to certain antibiotics is becoming increasingly available. Molecular testing is particularly useful for identifying levofloxacin and clarithromycin resistance because only a few specific mutations are responsible for almost all cases of phenotypic resistance. In many countries, commercial kits are available to test for resistance to levofloxacin and/or clarithromycin by PCR on gastric biopsies. The mutations responsible for clarithromycin and levofloxacin resistance can also be identified from stool samples. In a recent meta-analysis of 11 studies, including 592 patients, PCR-based analysis of stool samples accurately determined clarithromycin resistance in patients infected with *H. pylori* (124).

H. pylori resistance to multiple antibiotics can be simultaneously and rapidly evaluated by NGS. NGS relies on comparing the derived sequence data to a panel of well-characterized gene mutations predicting antibiotic resistance. Hundreds of reads per gene are obtained, allowing for the evaluation of possible heteroresistance (125). NGS has been optimized to provide data on

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multiple resistance-associated genes in either fresh-frozen gastric biopsies or from tissue sections taken from the formalin-fixed, paraffin-embedded tissue blocks that are routinely prepared for diagnostic endoscopic pathology (126,127). Recently, novel stool-based NGS testing has been shown to have a 92% concordance with gastric biopsy NGS results (128). Stool-based testing offers clear practical benefits when endoscopy is otherwise unnecessary, as in most cases of refractory *H. pylori* infection.

Comparative studies are needed to determine whether traditional culture, PCR, or NGS leads to the greatest rate of *H. pylori* eradication and with the lowest incremental cost. Molecular methods are likely to be most advantageous when the genetic basis of phenotypic resistance is limited to a few highly predictive mutations. A potential advantage of NGS over culture is that more than 90% of samples yield DNA for testing, much higher than the success rate of culturing *H. pylori* from biopsies in routine clinical practice. Ultimately, the choice between the different test modalities will be highly influenced by local experience, acquisition cost, and availability.

A number of studies have attempted to characterize the benefits of antibiotic susceptibility testing in treatment-naive and treatment-experienced patients with *H. pylori* infection. More than 40 clinical trials of empiric therapy vs therapy tailored to the results of antibiotic susceptibility testing have been performed over the past 2 decades. The data are challenging to compare because of significant heterogeneity in study designs, study populations, susceptibility-testing methods, and treatment characteristics. Most studies were conducted in the Western Pacific and a few in Europe, but none in North America. Furthermore, not all were RCTs, and some combined tailoring for antibiotic susceptibility with tailoring for PPI selection and dose based on a patient's *CYP2C19* genotype, to predict rate of PPI metabolism.

Recent meta-analyses report a small but significant advantage for antibiotic susceptibility tailored approach for first-line treatment (risk ratio 1.15; 95% CI 1.11–1.20 (129) and 1.14; 95% CI 1.08–1.21 (130)). However, in the subset of trials where empiric therapy was BQT or a nonbismuth quadruple regimen, no advantage was evident for tailored therapy. Thus, when BQT is selected as first-line empiric therapy and has a local eradication rate >85%, there is no need for susceptibility testing before first-line treatment. Optimizing BQT, as discussed above, and providing patients with anticipatory guidance regarding dosing and side effects can help to maximize success with BQT. Providers are encouraged to monitor success rates of the treatments they prescribe and consider using antibiotic susceptibility testing if eradication rates with their preferred first-line therapies are less than about 85%.

Recent meta-analyses of treatment-experienced patients with persistent *H. pylori* infection concluded that antibiotic susceptibility testing performed before second- or third-line therapies did not improve eradication outcomes compared with empiric treatment (129,130). This conclusion should be viewed with caution, given the limited number of relatively low-quality studies. For second-line therapy, only 5 relevant studies were identified, with approximately 200 patients in each arm (i.e., empiric and tailored), although the largest study did achieve statistical significance (131). For third-line therapy, there were only 3 studies. In the only large RCT (approximately 200 patients per arm), antibiotic susceptibility-tailored therapy demonstrated a 6% advantage over empiric therapy, but this was not statistically significant (132). All the above studies were conducted outside of the United States and used a variety of 7- or 14-day PPI-based triple regimens as their initial eradication treatment. These findings further emphasize the importance of factors driving treatment failure in the setting of confirmed antibiotic susceptibility (e.g., gastric acid suppression, adequate dosing of regimen components, and patient adherence).

In a large, high-quality study (133), patients in need of third-line treatment for persistent *H. pylori* infection were randomized to molecular or culture-based susceptibility testing. Treatments were tailored based on antibiotic susceptibility testing results. Eradication rates with tailored third-line treatments were similar between groups, but both were superior to historic controls treated empirically (88% vs 78%).

Based on expert consensus after considering the evidence limitations, we advise using antibiotic susceptibility testing when the choice of therapy remains unclear after taking into consideration previous treatments for *H. pylori* infection, past antibiotic exposure more generally (particularly use of macrolides and quinolones), and any documented history of penicillin allergy. This recommendation can be applied to treatment-naive and treatment-experienced patients with *H. pylori* infection. In particular, and based largely on expert opinion, we recommend antibiotic susceptibility testing before the use of regimens containing clarithromycin or levofloxacin. There is a clear unmet need for adequately powered, appropriately designed clinical trials to define how best to incorporate antibiotic susceptibility testing for *H. pylori* into clinical practice in North America.

PROBIOTICS AND *HELICOBACTER PYLORI* THERAPY

Recommendation

12. There is insufficient evidence to suggest that the use of probiotic therapy improves the efficacy or tolerability of *H. pylori* eradication therapy (conditional recommendation; low quality of evidence).

Numerous systematic reviews and meta-analyses have attempted to address whether probiotics improve the efficacy and/or tolerability of *H. pylori* eradication therapy (134,135). There are important challenges that can be identified throughout the probiotics studies, which include heterogeneity of study designs, lack of blinding, variability and lack of standardization of the probiotic formulations, use of obsolete *H. pylori* eradication therapies as the comparator group (e.g., PPI-clarithromycin triple therapy and treatment regimens lasting only 7 days), and a preponderance of studies performed in Asia. To date, no high-quality RCTs on this subject have been reported from North America.

A network meta-analysis included data from 40 studies and 8,924 patients with *H. pylori* infection (136). A modest eradication rate benefit was observed (RR 1.10, 95% CI 1.10–1.18), with a lower incidence of total side effects (RR 0.47, 95% CI 0.39–0.56). There was significant study heterogeneity with a wide range of eradication regimens, probiotic supplements, and durations of antibiotic and probiotic therapies used in the included studies. Probiotic duration greater than 2 weeks, and combining probiotics with BQT, was associated with higher eradication rates, when compared with shorter durations and combining probiotics with non-BQT regimens, respectively. Lactobacillus and multi-strain probiotics were associated with the highest eradication

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rates. The benefits of probiotics seemed to be most profound in studies from China.

Although the available data on the benefits of adding probiotics to the efficacy and tolerability *H. pylori* eradication therapy are promising, they should be viewed as hypothesis-generating rather than worthy of a formal treatment recommendation. Several important practical uncertainties prohibit a formal recommendation for their routine use in North America. Studies from North America are clearly needed as are greater clarity around the most appropriate probiotic strains, dosages, durations, and combinations with antibiotics that might benefit *H. pylori* treatment efficacy and/or tolerability.

FUTURE RESEARCH PRIORITIES

In preparing this CPG, we identified key knowledge gaps in the management of patients diagnosed with *H. pylori* infection or at risk of harboring *H. pylori* infection in North America, specifically, and these should be acknowledged as research priorities. One such research priority is identifying which individuals residing in North America are most likely to benefit from opportunistic *H. pylori* testing (and subsequent treatment if positive) to prevent gastric cancer, given that this so-called "test-and-treat" strategy has proven to be effective for primary gastric cancer prevention in some high gastric cancer incidence regions worldwide. Another research priority is to conduct additional high-quality studies in North America that compare the effectiveness and tolerability of the newly approved and recommended regimens to optimized BQT in treatment-naive patients. Studies that help providers select among the first-line therapies are also needed. One obvious unmet need is to evaluate these newer FDA-approved regimens in treatment-experienced patients with persistent *H. pylori* infection. The recent FDA approval of PCAB-based *H. pylori* treatment regimens in North America creates opportunities to evaluate new treatment regimens. For example, whether replacing a PPI with a PCAB in BQT or rifabutin triple therapy further improves the eradication rates of these regimens is an important clinical question. Moreover, further work is needed to understand how to optimize PCAB amoxicillin dual therapy in North American populations for both treatment-naive and treatment-experienced patients to achieve consistently high eradication rates. PCAB-based therapies have reminded us of the critical importance of gastric acid suppression in successfully eradicating *H. pylori*. North America is a melting pot of diversity, and this is mirrored in the genetic heterogeneity of the component ancestral populations. The prevalence of *CYP2C19* polymorphisms and, consequently, the impact on the metabolism of some common PPIs (omeprazole, lansoprazole, and pantoprazole), varies according to ancestry (e.g., people of Asian ancestry have a higher prevalence of CYP2C19 poor metabolizers). Further studies are needed to establish whether *CYP2C19* testing to tailor gastric acid suppression or perhaps empiric selection of non-CYP2C19 metabolized PPIs or a PCAB should be considered, and whether these options are cost-effective compared with the current standard of care, which is agnostic of patient pharmacogenomic profile. Along similar lines, antibiotic susceptibility testing also offers the possibility of an individualized, precision approach to treatment selection in patients with *H. pylori* infection. As discussed in Key concept 6, the optimal time to perform antibiotic susceptibility testing in treatment-naive vs treatment-experienced patients, as well as the incremental clinical and cost-related benefits compared with empiric therapy have not yet been evaluated in studies from North America; this is an immediate research priority, given the anticipated availability of molecular susceptibility testing on the horizon. Finally, as we increasingly use antibiotic susceptibility testing in clinical practice, every effort should be made to develop a national registry to track *H. pylori* antibiotic resistance rates for commonly used antibiotics and local eradication success rates with specific treatment regimens. Such information would help clinicians to make the most evidence-based treatment choices for their patients.

CONFLICTS OF INTEREST

Guarantor of the article: William D. Chey, MD, FACG.
Specific author contributions: K.B.G. and S.G.: methodology. All authors: conception of the guideline, creation of first draft, revision of subsequent drafts, and approval of final document.
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